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Joint Meeting of Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

THURSDAY, MARCH 11, 2010

8:00 a.m. to 2:45 p.m.

Hilton Washington DC/Silver Spring

8727 Colesville Road

Silver Spring, MD

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I N D E X

P R O C E E D I N G S

8:00 a.m.

DR. SWENSON: Welcome back to the second day of a joint meeting of the Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss and consider the design and implementation of a trial around the question of the benefits and problems of LABA plus ICS versus ICS alone.

It's now time to introduce ourselves again, for those new people here. So I would ask Dr. Hubbard, at that far end, to start and we'll come around the table in this direction.

DR. HUBBARD: I'm Richard Hubbard. I'm the Industry Representative. I'm a pulmonary-allergy critical care specialist from Pfizer.

DR. MORRATO: Good morning. I'm Elaine Morrato. I'm an epidemiologist at the Colorado School of Public Health, University of Colorado-Denver.

DR. CNAAN: Avital Cnaan. I'm a biostatistician at Children's National Medical Center and George Washington University.

DR. KRISHNAN: Good morning. I'm Jerry Krishnan. I'm a pulmonologist and epidemiologist and I direct the Asthma and COPD Center at the University of Chicago.

DR. MOUTON: I'm Charles Mouton. I'm a family physician at Howard University.

DR. PLATTS-MILLS: I'm Tom Platts-Mills. I'm head of Asthma and Allergic Disease at the University of Virginia.

DR. D'ANGIO: Carl D'Angio. I'm a neonatologist and vaccine researcher at University of Rochester.

DR. WOLFE: Sid Wolfe. I'm a general internist. I'm with the Public Citizen Health Research Group and I'm a member of the Drug Safety and Risk Management Advisory Committee.

DR. FINK: Bob Fink, pediatric pulmonologist, professor of pediatrics at Wright State University, Dayton, Ohio.

DR. GREENE: Bill Greene, Chief Pharmaceutical Officer, St. Jude Children's Research Hospital.

DR. BRITTAIN: I'm Erica Brittain. I'm a statistician at National Institute of Allergy and Infectious Diseases.

DR. KRAMER: I'm Judith Kramer, Associate Professor of Medicine, Duke University, in general internal medicine and chair of the Drug Safety and Risk Management Advisory Committee.

DR. SCHOENFELD: I'm David Schoenfeld. I'm a biostatistician at Massachusetts Children Hospital and Harvard Medical School.

DR. SWENSON: I'm Eric Swenson, Professor of Medicine and Physiology at the University of Washington.

DR. KHUC: Kristine Khuc, Designated Federal Official, Pulmonary-Allergy Drugs Advisory Committee.

DR. ROBERTS: Susan Roberts, epidemiologist and associate professor in the clinical research program, University of North Carolina-Wilmington.

DR. OWNBY: Dennis Ownby. I'm a pediatric allergist. I'm Professor of Pediatrics and Internal Medicine, Medical College of Georgia.

MS. WALDEN: I'm Angelica Walden. I'm a

patient representative, in quality management, from the Medical College of Georgia.

MR. MULLINS: I'm Rodney Mullins. I'm the Consumer Representative and National Director of Public Health Advocates.

DR. ROSENTHAL: Good morning. I'm Jeff Rosenthal. I'm a pediatric cardiologist and Professor of Pediatrics at the University of Maryland, School of Medicine, and I'm on the Pediatric Advisory Committee.

DR. JOAD: I'm Jesse Joad. I'm a pediatric allergist and pulmonologist, Professor Emeritus, University of California-Davis.

DR. FLEMING: Thomas Fleming, Department of Biostatistics at the University of Washington.

DR. CARVALHO: Good morning. I'm Paula Carvalho, Professor of Medicine, University of Washington, in pulmonary critical care.

DR. MCMAHON: Ann McMahon, Deputy Director, Division of Pharmacovigilance I in the Office of Surveillance and Epidemiology, FDA.

DR. DEL PAN: Gerald Del Pan. I'm the Director of the Office of Surveillance and

Epidemiology at FDA.

DR. CHOWDHURY: I'm Badrul Chowdhury, Director, Division of Pulmonary and Allergy Products, FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, Director, Office of Drug Evaluation II, FDA.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the Director of the Office of New Drugs at FDA.

DR. SWENSON: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care

that their conversations about the topic at hand take place in the open forum of this meeting.

We are aware that members of the media are anxious to speak with FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I would like to remind everyone present to please silence your cell phones and other electronic devices, if you have not already done so.

The committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thanks very much.

I'll now ask Kristine Khuc to read our conflict of interest statement.

DR. KHUC: The Food and Drug Administration is convening today's joint meeting of the Pulmonary-Allergy Drugs and Drug Safety and Risk Management Advisory Committees under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government

employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with federal ethics and conflicts of interest laws covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Federal Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant

waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, royalties, and primary employment.

Today's agenda involves discussions of the design of medical research studies to evaluate serious asthma outcomes, such as hospitalizations, a procedure using a breathing tube, known as intubation, or death, with the use of a class of asthma medications known as long-acting beta-2 adrenergic agonists in the treatment of asthma in adults, adolescents, and

children.

This is a particular matters meeting during which specific matters relating to long-acting beta-2 adrenergic agonists will be discussed.

Based on the agenda and all the financial interests reported by the members and temporary voting members of the committee, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Richard Hubbard is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry.

Dr. Hubbard's role at this meeting is to represent industry, in general, and not any particular company. Dr. Hubbard is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue.

Thank you.

DR. SWENSON: Thank you. Now, I'd turn the microphone over to the FDA for their opening remarks. Dr. Rosebraugh?

DR. ROSEBRAUGH: Thanks, Dr. Swenson. I'd like to welcome everybody back for a second day. I'm glad that everyone had the endurance to come back for another day of the discussion.

So I kind of wanted to just start out and sort of clear up a couple of things today that I think would help the panel in their discussion and to kind of give you a sense of where we think we need to head

with what we need to hear today, and the first is about the labeling changes.

So I'm going to try to go back into time to December of '08, to the last advisory committee meeting we had. And I should preface this by saying that anything that's happened longer than about 20 minutes ago, my memory is sort of questionable, at best. But fortunately, I have Dr. Chowdhury here, who, some would say, has a Vulcan-like memory and never forgets anything. So he can correct me if I'm wrong.

So the upshot of that meeting was that there were a lot of unknowns about whether steroids mitigated the risk or not and we should craft some sort of labeling that indicated that until those unknowns were resolved, people should try to limit exposure to LABAs, even in the face of steroids, to the extent possible.

So the basic concept we have with our labeling is that's what we're trying to convey, is that there are unknowns out there; and, so you should, to the extent possible, limit patients' exposures to

long-acting beta-agonists until those unknowns are resolved.

The exact wording of our language has not been finished and we will have discussions with the industry, but I would anticipate that that wording will not preclude us doing the safety studies necessary to answer that question, and that includes if people wanted a six-month trial or a one-year trial.

So I think that you should not worry about what the labeling will say. I think you should focus more on what is the study we need and we will make sure that the labeling will allow us to do that study. So that's the first issue.

The second issue is that while we do have healthy internal debate about study designs and ethics and that sort of thing, I think that I should just put out on the table that CDER feels that these are ethical studies and that we have equipoise and that these are questions we need to answer.

There are a lot of people on these drugs. They take these drugs a long time. Some are on for

many, many weeks to years, and so let's try to get the answer so that we know whether we are giving them correctly or not.

So with that in mind, I think the most important things for us to focus on are what are the questions, what study design will answer those questions, and what are the best endpoints, and that's kind of what we want to hear our dialogue about today.

Of course, if somebody has a big concern and they want to voice it, we're always happy to hear that, too. I don't want to shut that down. But I do want to get some of the answers on the trial design stuff today, because time goes quickly at these advisory committee meetings.

With that, I just want to turn to the other panel members and see if they have anything else that they want to add. Gerald, anything you want to say?

DR. DEL PAN: No. I have really nothing to add. I think we believe that studying these things is important.

DR. JENKINS: I would like to add just a couple of additional comments to echo some things that

Dr. Rosebraugh said yesterday.

For many years, people have expected that FDA should have the authority to require safety studies and for many years, we didn't have that explicit authority under the statute. But a couple years ago, Congress did give us that authority under the Food and Drug Amendments Act of 2007.

So we now do have the authority to require sponsors, in certain situations, to do safety studies to address significant safety concerns. And as Dr. Rosebraugh said, we have already, as a center and as an agency, determined that additional safety studies are needed for the long-acting beta-agonists to address this question about the combination use with inhaled corticosteroids and what the safety findings might be in that setting.

I think we've all agreed that we understand what the risks are when you're not using inhaled corticosteroids. Now, we believe there's still an unanswered question that warrants further study to better understand what is the safety when you combine the two agents with inhaled corticosteroids.

As Dr. Rosebraugh said, now that we have that authority, it shifts a significant burden to the agency in deciding what studies are needed, how those studies should be designed, how large they should be, how they should be powered, all those factors.

Historically, all those factors primarily are the risk for the sponsor, because if they're designing their drug development program and they don't design their studies correctly and they fail to show that their drug has benefit, the main risk is that they don't get their drug approved.

Here, we're now shifting the burden to make sure we do good studies to the agency, and that's why we're asking your advice, because we recognize this is a very complex situation, where you're actually trying to study an adverse outcome which is paradoxically the benefit that you're expecting these drugs to provide.

We heard some of that discussion yesterday. Well, wouldn't you expect these drugs to decrease hospitalizations for asthma exacerbations? And yet, paradoxically, that's part of the signal that we're concerned about.

So that's why we're asking your advice to help address this question. The studies that we're planning to require may have the impact down the road of changing how we use these drugs. As Dr. Rosebraugh said, our current thinking and our advice for the labeling is to use the drugs only when they're needed and when they're needed, use them appropriately.

So down the road, if we learn that when you use them in combination, there is no excess risk, then that could change and better inform the use of the drugs.

It was also interesting to me, as I listened to the discussions and the presentations yesterday, for a while, it looked like people were saying it was unethical to randomize patients to LABAs. Then, later, it became, well, it seemed to be unethical to randomize people to withhold LABAs.

So that, to me, sounds like a definition of equipoise; that we have such a controversy and unclear data, that half the room seemed to be saying you can't withhold the drugs and the other half seemed to be saying you can't allow a patient to be randomized to

receive these drugs.

So we're really looking for your advice on how to do the studies that will answer these existing questions and we're really looking forward to hearing the discussion today and your answers to the questions that we posed.

So thanks.

DR. SWENSON: Thank you. We now move to the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written and oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, the direct competitors.

For example, this financial information may

include the sponsor's payment for your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today here is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair, and thanks much for your cooperation.

So our first speaker, I'd like to invite Dr. Robert Lemanske.

DR. LEMANSKE: Thank you, Mr. Chairman. I'm a Professor of Pediatrics and Internal Medicine at the University of Wisconsin. I'm the head of the Division of Pediatric Allergy, Immunology, and Rheumatology there, and I'm representing the American Academy of Allergy, Asthma, and Immunology at this meeting.

I have done consulting work for GSK/Merck, AstraZeneca, and Novartis, and the academy sponsored my trip here in terms of paying for my travel arrangements.

I've been asked by the AAAAI to represent them by reviewing with this committee some of our views and concerns regarding the current FDA recommendations on the use of long-acting beta-agonists and how these recommendations may influence patient care.

Could I have my first slide? Thank you.

I will start by reviewing some bullet points that members of the academy put together regarding this meeting.

First, we recognize that the FDA must protect the public by examining safety, as well as efficacy of long-acting beta-agonists due to potential adverse consequences from their use. We do not believe that new safety data on the risks of long-acting beta-agonists have come to light since the publication of the EPR-3. And I also serve on the EPR-3 panel.

We do feel that there are new efficacy data that point to added clinical benefits from adding long-acting beta-agonists to inhaled corticosteroids in both adults and children since the EPR-3 was published. And I think you heard yesterday some of the work that has been performed by the Childhood Asthma Research and Education Network. A study called BADGER that I presented at this meeting in December of 2008 was just published last week in the New England Journal of Medicine, clearly showing that the best choice, the choice that gave the greatest probability of producing the best response in children not well controlled on inhaled corticosteroids was the addition of a long-acting beta-agonist.

Next. In considering risk-benefit ratios of asthma therapies, the potential adverse consequences of continued higher doses of inhaled corticosteroids -- and, as a pediatrician, this is of great concern to me -- must be weighed against the potential adverse consequences of losing the documented steroid-sparing effect of long-acting beta-agonists when they are discontinued. This is especially important, as I've already said, in children and, also, the elderly.

Newly designed studies should examine how to step down from LABAs, as proposed by the FDA. As you heard yesterday, the data that's out there would suggest that that's not a good decision, and there is presently insufficient data to make recommendations to patients and health care professionals at this time.

We discussed this at our recent meeting and it made no sense to us, from a clinical perspective, to take someone who may be uncontrolled on a low dose of inhaled steroids, add a long-acting beta-agonist, get control, and then think about taking them off of that if they're doing well.

If that is something that the committee feels is important, then, obviously, we need to do the studies to determine how we should do that in a safe manner, while maintaining control.

As you heard already, based on previous data, very large studies may need to be done to truly ascertain any potential adverse consequences of long-acting beta-agonists. If these studies are undertaken, attempts at identifying both phenotypic and genotypic risk factors should be examined, as well, as relevant biomarkers.

Finally, the FDA and professional societies should partner in assuring that the new FDA announcements do not adversely affect access to long-acting beta-agonists and combination therapies through restrictive pharmacy rules and reimbursement practices. This is extremely important in terms of not only dealing with control of asthma, but, also, in individualizing patient care.

Finally, the AAAAI looks forward to working with the FDA, other government agencies, professional societies, and patient advocacy groups to help clarify

appropriate asthma care recommendations, especially the role of long-acting beta-agonists.

I'd like to thank the committee on the part of the academy for allowing us to participate in these discussions. Thank you.

DR. SWENSON: Thank you, Dr. Lemanske.

Our next speaker is Ms. Nancy Sander.

MS. SANDER: Good morning. My name is Nancy Sander. I'm president and founder of Allergy and Asthma Network Mothers of Asthmatics, the only nonprofit organization whose sole mission is to eliminate death and suffering due to asthma, allergies, and related conditions.

We have 25 years of experience of award-winning service to patients. I have asthma, as do three of my four grown children.

By way of disclosure, I paid my way here. We don't sell our logo. We don't endorse or certify products or companies. If you want additional information, there's a whole page in your packet there.

Allergy and Asthma Network Mothers of

Asthmatics strongly opposes FDA's recommended label changes for long-acting bronchodilators, as it is premature and will prejudice all future studies and use of an entire class of medications known to benefit patients nationwide.

We also take exception with the FDA's demands to reduce the number of canisters dispenses, as if we and our physicians are incapable of making decisions about appropriate therapy.

Regardless, FDA's proposed label really screams "warning-asthma deaths" to patients and it will likely have the prescription-dampening results the agency seeks, as fear-ridden patients, prescribers, and insurers abandon what FDA calls "killer therapy."

On one hand, FDA warns that LABAs are dangerous and orders us to use less of them. On the other, FDA orders manufacturers to do more safety studies with our children and us as adults. But it seems, in this case, that FDA put the cart before the horse.

Shouldn't studies come first and label

changes second? My daughter participated in a 14-month drug study program 27 years ago. It changed our lives and it's the reason why I founded this organization. But the study drug wasn't labeled "warning-asthma deaths," or we wouldn't have participated.

FDA's warning doesn't belong on the drug. It belongs on the disease. Ten people die of asthma every single day and sometimes we talk to those families of loved ones who have died and I can assure you, they have never come to us and said it was the medication that killed them.

Asthma deaths happen when people underestimate asthma's insidious propensity to rob the body of oxygen, as inflammatory cells rupture and release toxic fluid into mucous-plugged airways.

Asthma deaths are declining at a time when LABA use and adoption of NIH guidelines are at an all-time high. FDA was there for the guidelines, helped develop and approve the guidelines, and there have been no new clinical peer-reviewed studies to justify FDA's drastic new approach.

To the contrary, BADGER, as we just heard, confirmed that long-acting bronchodilators are appropriate as add-on therapy.

I'm going to skip right to the end, because I'm running out of time. But all asthma medications have risks. So in formulating a new study design, remember that medications are only one part of what must be a comprehensive action plan developed in consideration of relevant allergens, irritants, and secondary or coexisting conditions.

We recommend observational, real world EPR-3 studies, but these studies will not happen if frightening labeling says "warning-asthma deaths."

Thank you very much for this time.

DR. SWENSON: Thank you.

Our next speaker is Dr. Bobby Lanier.

DR. LANIER: Thank you, Mr. Chairman. I'm Bob Lanier. I'm a pediatric allergist. I'm the Executive Director of the American College of Allergy, Asthma, and Immunology, 4,000 of us who write asthma drugs, see them during the afternoon, and answer the phone at night. We have a little bit of a pulse on

who's who.

Disclosures, I own no stock; I do not do promotional speaking; I have no consultancies; and, I paid my own way here to represent the college.

I came to this meeting to give this committee a sense of what the practicing physician has and related in reference to the recent press release and the suggestions for label changes. I can sum it up by saying we don't support it. We don't believe it.

Because of that, you need -- there is a big communication gap here that needs to be filled. We did a blast e-mail to our membership the day of the FDA release and the leadership -- I wrote the e-mail for both the college and the academy and said that we could live with the label changes, as suggested, provided we could follow-up.

At that point, we began to get Tweet'd, Facebook'd, e-mailed, phone called, and just deluged with members saying that we hadn't taken a strong enough stance.

So last Thursday, we took a poll of the

membership. And granted, when you do e-mail polls and so forth, you don't get as big a volume as you would like. We got about 10 percent of our membership to respond. And I gave them three potential positions.

The first position was to say we support the FDA label changes and can live with it. The second is we're concerned about the fact that the FDA is concerned, but not enough to change our pathways. Three, those drugs are dangerous, should be prescribed only by specialists. And, fourth, we gave them the option to say if those positions aren't your position, then write us one of your own.

Here's the results. Not a single member supported the FDA label changes, as they're written. Sixty-four percent said that they thought that they -- they were worried that FDA was worried, but not enough to change their current prescribing habits, because of NHLBI guidelines.

Two percent said that the drug should be given only by specialists, and 34 percent of the people who responded took the extraordinary step of actually writing down a comment. And if you know

doctors and how difficult it is for us to get a poll response or a response to anything, you know that's pretty big.

Now, the results of that, I'll try to sum them up for you. I have them here for you, if you want them. They're kind of inflammatory and I didn't think I wanted to leave them around on a table, but I did bring them for you.

The sticking point here is the drugs we dropped after control was met. Now, my friends, we think that's the vision of a 17-year-old boy with asthma -- take them until you feel better and stop them. That's what we've dedicated our lives to stop. That's called step-off therapy.

If you look at the refill rates on drugs, that's what people do. They only refill them four or five times a year. That means they're stepping off. Maybe patients are protecting themselves with noncompliance.

There's a lot of terms we've heard in the last couple of days, step-up, step-down. Here's another one -- step off. And then the one that we

think FDA will eventually put into the armamentarium, which is step back. Step back to steroids; step back to increased incidence.

What we are concerned about is there's a problem there, too. If you take an allergic child that's got allergy and asthma, they're going to have 50 years of steroids. They inject them. They've got bubblegum-flavored steroids now. You get nasal steroids, inhaled steroids, topical steroids. There's a big concern about the long-term effect of steroids. At least we know these are cumulative. We don't know that about beta-agonists.

So in this particular study that we're looking at, we're not going to get results for five to six years. And in the interim, we are stuck, doctors and patients, with the labeling anxiety that goes along with these warnings.

Everything we have has a warning on it now. The warnings, black boxes, they're just cheap now. Every one of them has got it, and we're a little concerned about that.

The final thing, I'll say that you will not

have a buy-in from the physicians in this country until you see better data generated than what we've seen so far. We will resist you. We don't mean that in a bad way, but there is a disconnect in communication.

Thank you very much.

DR. SWENSON: Thank you. Our last speaker -- is Dr. Teague here? Yes, good. So Dr. Gerald Teague.

DR. TEAGUE: Good morning. My name is Gerald Teague. I'm a pediatric pulmonologist. I'm Professor of Pediatrics at the University of Virginia. That is my employer.

Eighty percent of my salary is covered by the National Institutes of Health. I do speak for Merck and I do retain honoraria from those events. I'm here on behalf of the American Thoracic Society. They have covered my expenses in attending this meeting, and thank you for the opportunity.

I represent the 15,000 physicians of the ATS, and we, first, thank you for the opportunity to comment upon clinical trial design to evaluate

outcomes with use of long-acting beta-agonists in the treatment of asthma.

We were founded in 1905, and since then, ATS members have conducted numerous clinical trials into the causes and treatment of asthma. We, furthermore, appreciate the thoughtful analysis that's been done by the FDA, which suggested increased mortality in children and adults treated with LABAs.

We, furthermore, agree that the use of combination therapy, that is, LABA with inhaled corticosteroid, is critical to the safety of our patients. And we also agree that LABAs are not meant for use in isolation or in the treatment of nonspecific symptoms.

Although we support the concerns raised by the FDA, we respectfully submit, though, that the proposed label change, which advises to stop LABA use alone as soon as possible and maintain asthma control with inhaled corticosteroids alone, as per the previous speaker's comment, just isn't supported by scientific evidence.

The practice advisory of the FDA competes

and actually clouds national guidelines, which have been developed by professional societies. And we emphasize that there are just very few published data to support this rapid step-down approach.

The proposed label change is inconsistent with the FDA-proposed conduct of a clinical trial. We heard the comments this morning already made about that, but it does concern us.

Thus, ATS strongly, strongly supports further studies into the safety and efficacy of LABAs and we think the following features should be inherent to the trial. First, we propose an appropriate sample that includes both children and adults and that is large enough to address safety, including mortality and the severe events reference, like hospitalizations, in LABA-treated patients.

Second, that participants in the trial should be thoroughly characterized, first, to exclude individuals with COPD. We think that is just as important to identify asthma patients who benefit from add-on LABAs, as well as those who suffer adverse events as a result of LABA treatment.

Third, we ask that you consider a three-arm study, which tests both short-term and long-term use of LABAs and, also, addresses the safety of LABA withdrawal in those patients who have been on LABA combination for some time and have had good asthma control. Is it safe to abruptly discontinue the LABA?

Fourth, we ask that you define surrogate endpoints for asthma mortality, such as hospitalization and/or severe exacerbations, as would be defined by recently issued professional society statements. A trial with mortality alone as the primary endpoint would be lengthy, involve massive numbers of participants, at a very high cost, and may not answer the critical question.

So, finally, we recommend just two points. One, an ongoing partnership between the ATS and FDA in studying the safety and efficacy of LABA and inhaled corticosteroids in adults and children with asthma. Such a partnership would include the design of clinical trials.

Second, we ask that the FDA move very cautiously with labeling changes. A revised label

should inform providers and patients of the risks of LABA monotherapy, as well as the benefits LABAs can play in establishing asthma control.

We ask that we investigate the potential risks of long-term LABA combination therapy -- that is, the potential corticosteroid toxicity -- and the risk of discontinuation of LABA abruptly from a well controlled patient.

I thank you very much. I do have the official statements of the ATS here for your package, if you need it. Thank you.

DR. SWENSON: Thank you, Dr. Teague.

At this point, I thought it might be helpful to at least give an overview of the rest of the day, as I see it.

We left a number of people with questions yesterday for further clarifications from the FDA and from sponsors, and I thought we'd spend the next block of time at least catching up on most of those. We have a list of people that wished to speak yesterday and we'll proceed through that.

Then following that, the FDA has provided us

with seven questions that we'll take in turn. And for those that will be speaking in this first portion here on further clarifications, if your question really focuses down quite nicely with one of these specific questions, then perhaps you could wait. I'd like to leave this first part open for more general discussion.

So to begin that, Dr. David Schoenfeld was our last speaker.

DR. SCHOENFELD: So I had a question really of the three different industrial groups. Looking at this, it seemed to me that the real issue is around deaths and intubations, because it seems to me that the hospitalizations -- the meta-analyses are convincing that, in fact, there's a benefit there. So that the chance of it really telling us anything new is small.

I also would worry, if I was in the industry and doing a study with 8,000 patients, that there be three deaths and that they'd all end up on the LABA group. And that has a 12.5 percent chance of happening, by the way. It's not that likely, but it

could happen.

Then when added to all the meta-analyses, it will just sort of add grist to the fire that already is lit and not really allow us to know the safety of the drug. And agreeing with Thomas Fleming, I think what you need to rule out is something larger than a 1.25 increase in risk.

So I was wondering. I did a back-of-the-envelope calculation that if each of you did a study with 25,000 patients, each of the three sponsors, one, you would be able to rule out an absolute risk of 2 in 3,000, which is the risk estimate that basically has been estimated for these drugs.

You'd be able to rule that out. And if nothing happened strange about the three studies, if they all pretty much showed the same thing, when we combined them all, we would have 75,000 patients and we would rule out a risk of 1 in 3,000, which is sort of the absolute risk that faces patients now.

So, really, it's sort of people live with this risk and it would just add that much risk. I don't know. I guess it's up to the physicians and the

patients to say if a 1 in 3,000 risk is too much or not for the benefits of LABAs. I won't comment on that, but it just seems reasonable to me as a starting point.

So the problem is, are these three studies feasible, with the assumption that they are going to be done at exactly the same time, so that they will compete with each other for patients, basically.

Also, I know how multicenter clinical trials are done. They also will compete with each other for institutions, because you basically go out and get a bunch of institutions. And so there's that competition, too, because one institution would only be able to do one trial, probably.

So I guess I think it's worthwhile to have the industry representatives inform us as to whether they consider this feasible in a reasonable amount of time, and I think reasonable would be, roughly, five years, because I would hope that your companies are trying to develop even better asthma drugs as we speak and that there is some pipeline and the LABAs are not -- these three LABAs, at least, and LABAs, in general,

are not the last word in asthma control forever.

DR. KNOBIL: Kate Knobil, GSK. I think you bring up some really excellent points, because these are some of the questions that we've been wrestling with in trying to do such a trial.

Since we found the results of SMART, we've been trying to find a way to address these questions. And while, in response to Dr. Fleming's question, I think that we probably could look at a risk to exclude that's greater than 25 percent, but even then, based on the numbers that we had, since we had to impute a rate, we had no deaths with Advair, our rate is extremely low.

But it might be useful to share some of the challenges that we faced with SMART, which, as you've heard, we enrolled 26,000 patients, if that's something that would be useful to let you know what we had to do to get those 26,000 patients, it might put some of this into perspective.

So SMART, as you heard yesterday, was in two phases and the first phase was a media campaign. And what we did is, in that first phase, we contacted over

11,000 physicians, and we projected a need of 750 to enroll 30,000 patients, when supported by the media.

Of those 11,000-plus investigators, 915 were interested in participating, which is about 8 percent. Fewer than 500 achieved IRB approval. And those 487 sites enrolled about 15,000 patients.

With that media campaign, it was estimated that we reached about 70 percent of patients with asthma in the United States. So what the media campaign did, it had an 800 number; if someone was interested in participating, they called the number and they were directed to the site. But even with that, we were only able to achieve 13,000 patients.

In Phase 2, we contacted over 50,000 physicians, and, at the time, there were approximately 250,000 physicians in the United States. And so the total number of responders from that was approximately 6,000 and those that actually ended up getting IRB-approved and regulatorily-approved was about 5,600.

Then of those 5,600, only about 50 percent enrolled one patient or more. So of those that did enroll patients, each site enrolled about four

patients per site.

So as you can see, even if you go beyond the usual way that we do clinical trials, the enrollment of this number of patients is really quite difficult.

Just to remind you, again, SMART was very different. SMART was only a single visit. It wasn't as if these patients were being followed on a regular basis, every two months, every three months. This was just a single visit, history and physical; patients were given their drug and were followed-up by telephone contacts.

So yesterday, after the conversation, we did do a power calculation or a sample size estimate of if we excluded a risk of 4, as Dr. Fleming recommended, it would take about 115,000 patients, with our numbers, with Advair.

To your other question, if we were to enroll these studies all at the same time, 25,000 patients, I think this response would be even lower, especially since we're studying death. So, again, in the informed consent, we'd have to say that we're investigating the risk of asthma-related death.

So those are some of the challenges that I think we face.

DR. BONUCCELLI: I think Kate said most of it. Cathy Bonuccelli, AstraZeneca. So I don't think I have to talk for a long time. I think we could show you, again, this picture, which we showed in the core presentation yesterday, which was just our estimate of feasibility.

The gray bars are feasibility for various trial sizes if there was just one study running. The orange bars are if there were three studies running in parallel. So we don't have 25,000 up here, but we have 31,000, and we anticipated that would take probably greater than 15 years to complete. So I think that gives you a view.

To your other comment about additional products in the pipeline, yes, we do have other products in the pipeline for asthma. And, again, these would compete for those patients, as well, because we're trying to meet unmet medical needs. So we're also at the severe end of asthma in those studies, as well.

MR. PASCOE: Steve Pascoe, Novartis. We agree with your numbers, Dr. Schoenfeld, but we also agree with the comments of the other sponsors that a study of that proportion would take something on the order of 15 to 20 years, assuming the initiation rate could be maintained.

In practice, I don't think we have a precedent for this and our opinion is that the study, in the end, would fail. I think the most precedent point, however, is the impact a study of this magnitude would have on future research, both from an industrial point of view, where ability to compete, putting other molecules into these patient groups would be severely impaired; but, also, for other people wishing to undertake studies, the patient numbers I don't think would be there to do meaningful work.

So we would have great concerns of the significant impairment of potential future advances.

DR. SWENSON: Dr. Krishnan?

DR. KRISHNAN: Great. Thank you very much. I had a question for GSK and I was wondering if Dr.

Camargo could help address this question or perhaps Dr. Knobil.

The question I have is that we're being faced with helping, provide advice about studying an extremely rare event, the magnitude of which is not entirely clear. And I thought Dr. Camargo provided a reasonable justification for thinking about alternate study strategies.

Then he went on to say that while there are concerns that exist with observational study designs, there are also approaches to mitigate them. And I wanted to hear a little bit more about the nested case control study design and perhaps what exactly is known about ways in which we can appropriately account for confounding by severity.

Just to add a little bit more context to this, I think what he shows is a number of risk factors that have been associated with mortality and these could be inferred as ways to adjust for severity. I think that's one thing, but, actually, what we really need is a very good risk index or some sort of validated score in order to adjust for

confounding by severity, and I was wondering if you could talk to that.

DR. CAMARGO: Carlos Camargo from Mass General Hospital. Dr. Krishnan, in response to your question, you asked about confounding for severity and the importance of that to any observational effort.

I just want to preface my comments that I completely agree that the trial that Dr. Schoenfeld introduced here, the concepts, is a lovely one. I love clinical trials. I support clinical trials. I do clinical trials. I think it's not the way to do this. Rare events should be studied. I have learned throughout my career, in multiple schools, with observational studies like these that I'm about to talk about.

These studies were done in response to a true asthma epidemic, where there were clearly more deaths happening. It was unexplained. It was emergent. Something had to be done. The case control studies identified the harm. The product was removed. The death rate fell.

One of the most peculiar things about this

whole discussion is that this asthma epidemic that we are so concerned about is actually an epidemic of decreasing deaths.

The amount of deaths that have dropped over the last 10 years is extraordinary, and it's actually a big victory for allergists, pulmonologists, mothers of asthmatics, all kinds of groups that have been working to fight this problem.

Having said that, our epidemic could be studied, I think, most efficiently with these designs. And in contrast to Dr. Fleming's comments about the treachery of doing observational research, these studies work. We're now 20 years later, with a whole set of new approaches and understanding about how to make these studies work.

If you'd like a nice historical overview of this issue, I would point you to an article by Neil Pearce in the Journal of Clinical Epidemiology, 2009, nicely summarizes the experience in 1990 or so and all the things that we've learned in the ensuing 20 years.

Again, you have odds ratios of 1.6, 2.0, 2.1. The way they took care of confounding by severity

was by using a control group that was hospitalized for asthma. That was pretty crude. But note that in these studies, albuterol was not associated with risk.

So a rather simple approach to confounding by severity was able to show correctly that albuterol does not cause any risk. And that is an opportunity to correct, I think, a misstatement yesterday, which was that there's some sort of class effect with beta-agonists.

That's not true. There is no evidence, no credible scientific evidence that albuterol causes asthma death. It's been studied with the beloved randomized control trial and published in the New England Journal, showing that regular use versus intermittent use does not increase risk.

What was unique here was fenoterol. What was unique in the 1960s was isoproterenol. And perhaps what's unique is LABA. I don't think so. But what we would do to control for confounding was not just this simple approach, but, also, you could, for instance, restrict the sample to just people who had received inhaled corticosteroids of a certain number

of dispensings. You could also then measure a whole series of factors that relate to the likelihood of getting Advair or getting death, create propensity scores. These are things that weren't done 20 years ago.

All of these options -- and I know the epidemiologists in this room know this. All of these options are available to look at this issue in multiple different ways and look for a consistency of response, and that's going to be a key factor here, a consistent response. But before that's possible, you have to at least entertain the idea that rare events can be studied with case control studies, and that's what I've always thought to be true.

I'll just close with a final comment that one of the things that we all hold to be true, and it's been said numerous times in this meeting, is that the regular use of inhaled corticosteroids are one of the few things that we can do to prevent asthma death.

I would just remind you that that finding came from observational research. Thank you.

DR. SWENSON: Dr. Kramer?

DR. KRAMER: I have a question for Novartis and a comment to GSK, as well. The question for Novartis is, I noticed that in the background packet, your proposal for a study did focus on the full pediatric population from ages 5 through 17, and, yet, yesterday, in your proposal, you suggested that you only study adolescents.

I'd like to understand the basis for that, given the advice from the December advisory committee that we need more information on pediatric patients to be able to understand the benefit-risk ratio.

Could you just explain?

MR. PASCOE: So we believe that both populations are potentially important to study. I think our ethic is that we should concentrate our efforts to where we can add new data.

In response to the agency's positioning of the single agent in pediatrics, as well as the proposal for the fixed dose combinations direct study in pediatrics, we saw an opportunity there to contribute to a study solely dedicated in adolescents.

DR. KRAMER: But why do you feel that you

shouldn't contribute to the pediatric investigation, the younger pediatric age group?

MR. PASCOE: No. I'm not saying that we shouldn't contribute. We should. What we're saying is given our task was to propose one study design, we see both as relevant; but if we had one we could consider a higher priority, given the environment, then our choice would be adolescents.

DR. KRAMER: Why is that?

MR. PASCOE: Sorry?

DR. KRAMER: Why is that a higher priority? That's what I'm trying to understand. We have so little information.

MR. PASCOE: Okay. So if there are studies being done in pediatrics, no study solely in adolescents, to do a study in adolescents would seem to be more pertinent than to do another study in pediatrics.

So it's not prioritizing one patient group above another patient group. It's trying to marry the research effort so all the patient groups are addressed.

DR. KRAMER: Okay. And my comment to GSK, again, has to do with this issue of the proposal for an observational study design. I have to say that my basic point of view is that I share Dr. Fleming's concern here, when we're trying to really get a definitive answer, quantitating a causal relationship.

I'm a little -- I'm quite concerned, actually, knowing something about this, having participated in observational studies myself and a recent one with 50 million patient years covered. The proposal, I think, underestimates the difficulties for the study you propose.

For one thing, in your packet, you described requiring approximately 1,500 cases of death, and you propose actually putting together -- in the background packet -- putting together a collaboration with literally all existing data sources across government, health plans, the whole list.

You used, as an example, or the justification was that, well, the FDA is doing this with Sentinel; but if you know the details of that, we're really at the beginning stages. And I've been

through many conversations with the methodologists about the challenges of truly getting enough in these claims databases -- getting enough clinical data to be able to truly match controls. You don't even have things like smoking available in these claims datasets. And I just have some serious concerns about whether you could do what you're proposing that you could do.

Anyway, maybe you want to comment.

DR. CAMARGO: Please don't let my enthusiasm for the study hide the fact that I'm also a little nervous about taking this on. But this is a tough choice that we have before the committees.

It would be great to do a trial. I just don't think it's possible. So do we set off on this -- might I say -- fool's errand and block research on other products, scare patients, et cetera, et cetera, et cetera?

I learned in medical school and in a master's program and in a doctoral program and all the steps along the way and have propagated since to my own students rare events are studied with these kind

of approaches.

So to your point about could we get enough patients, well, we estimate that we actually could and these are the datasets and we've actually approached these different groups to get information about what they have. That doesn't mean they'll play.

But I'm pretty confident if this committee tells the FDA, "We're not thrilled by it, but this is probably the best option," and the FDA says, "This is the best option," you're going to get a big boost in the arm for your efforts, with the DEcIDE, with all of this infrastructure for this kind of research.

Again, this is aiming at an odds ratio of 1.25. If we accept Dr. Fleming's position, it would be much more feasible to do the study.

DR. KRAMER: I omitted to mention something really important. Not only do you have to get all these groups to participate, but there are deficiencies in terms of what you're looking for.

You required in your study design that they have a year of information before the index date, and that would presume, if you want to follow them for a

period of a year, that you have people with these sorts of periods of time in the datasets.

We know that there's a tremendous amount of turnover in the managed care environment and health claims databases; maybe not so much in VA and Medicaid. But if you need all of them and you combine the deficiencies in terms of clinical data to match and if you combine the difficulties with getting the population, I just think your timeline that you put down of being able to start and complete this within three to four years is quite questionable.

If you look at Sentinel, it's been proposed for two years and we're in a pilot stage now and we are limiting -- we are not doing the kind of study you're proposing. There's a lot of development to get to the point where you can just gather the data.

Finally, the analogy you gave with Dr. Pearce's publication, I actually had the opportunity to read his book about the fenoterol story, and I think you've really distorted that a little bit, because you were dealing with a -- you talked about drugs, but you didn't mention the dose effect.

The reason there was such concern here is you not only had nonselective agents, but you had, with isoproterenol 40, an 8-times dose effect. With fenoterol, you had the equivalent of 4 times any of the other products on the market, and you had noticeable death rates that were being detected in observational studies.

We have here, as you said yourself, a decrease in death rate and you're going to detect this. I'm not trying to bash observational studies, I think they're very appropriate in detecting signals, but when you want a definitive answer, you have to be realistic about what you can do and the time frame you can do it, and I think you've distorted that.

DR. CAMARGO: Well, let me respond to that, please. One, to the issue that I have distorted what Neil Pearce has said, I take strong exception. You might be interested to know that I actually did my sabbatical with Neil Pearce in New Zealand. I read that same book as it was being written.

I'm pretty familiar with the issues in New Zealand and that epidemic, which was truly an

epidemic. We don't have that. We have a good epidemic -- the epidemic of absence of death.

With regard to the challenges of these studies, they're there. I've already alluded to them. I know they're there. But this is for a target of 1.25 and I've already heard several times that it would be fine to look at a target of 2.

Finally, I would just say that for every criticism you can make of the observational studies, we do believe it for some things, for instance, benefit from death for asthma, highly relevant. I love the fact that you're focusing on death and not oral corticosteroids bursts or ED visits or any other number of surrogate and, I think, largely unrelated issues.

But let me just close with an example that I think may reassure some of the members. When inhaled corticosteroids were being introduced at higher doses, there was a concern from the FDA about non-vertebral fractures in the elderly.

So to address this issue, studies were done in four different populations using this methodology,

in the VA, the GPRD, in the Quebec Elderly Health Care, in United Health Care. All of these observational studies showed no risk at the label doses.

Trials since then looked at bone BMD measurements and they didn't have enough numbers to look at fractures, but they were completely consistent with this. This evidence was part of a decision to approve these products and subsequently has been borne out to be okay.

So these approaches have been used by the FDA. They can be done. It won't be easy. But I think the alternative, which I really like Dr. Schoenfeld's vision, is even harder. That's why you keep meeting. That's why these guys keep getting called up here.

I'm trying to propose an alternative, which doesn't maybe preclude other approaches, but I think should be pursued, and, ultimately, my opinion is that it's the most worthwhile pursued. But that's for you to decide.

DR. KNOBIL: Kate Knobil, GSK. I was going

to make the last point, again, that we agree that there are challenges to such a study, but we actually believe that they're more likely to be overcome than the challenges trying to do a very large randomized controlled trial of asthma-related mortality.

So it's really about what do we think we can get out of it and what do we think would actually have the best probability of success.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: Can I ask Dr. Camargo a direct question? We actually do have an epidemic of death in the United States, which is occurring in minority populations living in poverty.

There are now calculations suggesting the death rate may be as high as 8 times among affluent white people. The question for you is could you focus a study of the kind you're describing on that population. That's a population in which prospective double-blind controlled trials traditionally have not been done at all and, if you use the kind of normal recruiting practices of the companies, hardly get enrolled at all, could you focus your kind of study on

the population where there is actually a real problem in the United States today?

DR. CAMARGO: This is Carlos Camargo, again, in case you forgot -- for the transcriptionist.

[Laughter.]

DR. CAMARGO: I really hesitate -- one, I agree with your comment. I would point out that the highest rates of asthma mortality are actually in Puerto Rican-Americans and certain groups of Hispanics. There are other groups of Hispanics, for instance, Cuban-Americans, that have no elevated risk at all compared to white individuals. So there's a complex story in there and there's no question of a disparity.

I thought Mr. Mullins' comments yesterday about the importance of including all types of Americans in these studies, all types of people, let's get the data wherever we can get it, is a critical one.

To respond to your question, though, this committee has to say this is a viable approach, it's a feasible approach. It has to recognize that it's been

used before for exactly this issue.

Once that recommendation has gone forth and the FDA, I hope, would listen to this committee, the FDA has certain abilities and powers to get things done, and I think that's critical to the success of what I'm proposing.

Now, part of that would be to figure out, once there was a commitment to go in this direction, what is the availability of race and ethnicity data in these different datasets. We know it's not available for some, in fact, I would even say most, but it is available for some.

So once there's a commitment to move in that direction, these issues will be investigated, with the authority of the FDA behind it and your stamp of approval, and we'll get some of these answers, or we can continue to talk about randomized trials, which I do think is a bit of a fantasy.

DR. SWENSON: Dr. Morrato?

DR. MORRATO: Thank you. I'll just ask one question that relates to this discussion. I'd like to turn it back maybe to involve the FDA in part of this.

I know it started in your discussions, I believe, in December with them and that you were preferring a randomized control trial.

In light of what we've heard from Dr. Camargo and others around the table in terms of the pros and cons of a randomized control versus this case control, maybe it would be useful to share your thoughts around why you were against that as a design in terms of a case control and why you really only wanted randomized control trial data.

DR. ROSEBRAUGH: I'm going to start out with that. I think, for all the reasons that you've heard, we're always -- when we are trying to get precise estimates, we like randomized trials.

So when we started having these discussions internally, of course, there are a lot of obstacles to either kind of these trials as you discuss them. So that's sort of why we are here.

I'm not going to say which way I would want to go. I want to hear what the panel has to say about it. But as far as why we would like to have that, for the most part, we tend to make regulatory decisions on

randomized trials; not always, but for the most part, that's what we do, because we get the best estimate.

DR. MORRATO: So if I understand it, that's the preference, weighing the pros and cons of the feasibility and so forth in terms of the timeliness of having data to make regulatory decisions. That's really what you're looking for from the panel to discuss.

DR. ROSEBRAUGH: Yes. Certainly, it has to be feasible to be able to do it. So we always weigh that in. Convenience is not an issue with us. It's feasibility.

DR. SWENSON: Dr. Krishnan?

DR. KRISHNAN: I'd like to follow-up on that a little bit, because I think that the discussion is largely focused on clinical trial design and I think you're not going to find much resistance on the committee saying that that's probably the preferred design, when feasible.

However, we're also hearing there are unintended consequences of proposing that, including potentially sucking air out of the ability to do other

studies that might actually delay the development of products that are even more beneficial than the ones we are actually talking about today.

So can you give us a little more insight here on the FDA's experience with case control studies for the kind of problems we're talking about and where you've seen problems or experience that we should be taking into account as we think about what study design is appropriate?

So from your side, what are some of the problems you've seen with case control designs that perhaps Dr. Camargo and others have been talking about?

DR. ROSEBRAUGH: I'll probably let John sort of address that a little bit. I was going to back up to your question about would this delay development of other drugs.

It is always hard to anticipate whether that would happen, but I will tell you, there is quite an incentive for sponsors to get drugs developed and they usually do find a way to do that.

DR. JENKINS: Actually, Gerald, you may want

to comment a little bit more about case control or observational design. I think what I would add is we have to look at the hierarchy of evidence and, generally, the randomized prospective control trial is viewed as kind of the gold standard and observational studies are generally somewhere below that.

I think it also goes to some of the points people have made around the table about what's the effect size that you're finding. If the observational effect size is 1.5 as the relative risk, that's probably a lower level of evidence, in most people's minds, than if you find something that's five-fold increased.

So I think those are all factors we have to take into account as we're trying to decide. I think, also, you have to understand the world we live in. This controversy has been swirling around these drugs for now, what, 15 years since the SNS study was first made available, and we have to try to think about will we get an answer that's definitive enough to try to put this question to rest or will we get an answer that will still be subject to attack or scrutiny.

It's clear from the discussion yesterday and today, we've got some people who believe these drugs are very dangerous and shouldn't be available. We've got other people who believe these drugs are very valuable and important to the treatment of survival of patients with asthma.

Yet, we still have this lingering question about do they have an increased risk when you take them with combined inhaled corticosteroids. So it gets to how definitive of an answer can we get, how practical is it to get that answer, and merging all those together with trying to do the best we can.

I should say, under the authority that I mentioned earlier, the new amendments to our act from 2007, we can also require observational studies. So we don't just have the authority to require controlled clinical trials. We can require observational studies.

So if the consensus of this panel is that we'd love to have controlled clinical trials and they're not feasible or practicable and we recommend you take an alternative approach, we want to hear that

guidance.

Maybe, Gerald, you want to talk about some issues with case control studies.

DR. ROSEBRAUGH: Let me just add something real quick before Gerald does, and it's a follow-up on what Dr. Jenkins just said. So I think it is an important part. There are a lot of controversies around this and when the results come in from the study, the folks that don't agree with those results will tend to attack them. So we have to be able to have some assurance that it was a well-defined study.

Now, we have randomized trials that look like good control trials that have come in that have opposite results for meta-analysis and people still attack those. So as John said, we live in an environment where we have to be able to defend things.

DR. KRISHNAN: Right. I just want to point out that the SMART study, which was a randomized trial, had a variety of issues that muddied the water. So it's important to recognize that the study design, by itself, doesn't obviate concerns about designs or issues of interpretation.

But I'd like to hear not so much the general concept of limitations of case control designs. I think we've heard those and I think panel members are generally aware of those. What I want is more specifics about, on the FDA side, where case control studies have helped, where have they not helped, and perhaps some insights as to concerns you would have about applying it to this very specific question.

DR. DEL PAN: This is Gerald Del Pan. I'm from FDA. We believe that, first of all, observational studies, be they case control or observational cohort studies, are an important part of the armamentarium we have in post-approval drug safety surveillance.

Toward the end, we've had increased funding from them. We are working on guidance development for best practices for observational epidemiologic studies for drug safety questions using administrative health care databases, the kind GSK showed on their slide.

But it's not a one-size-fits-all issue here. So one area where we're using this is for a rare event, where we really believe clinical trials would

not be feasible at all, and that's to study the risks of cardiovascular disease with drugs used to treat attention deficit hyperactivity disorder. We don't really see any alternative to that.

We've had to pool a lot of databases to do that and we think that's the best way to go about that problem. We also have some experience with case control studies for thromboembolic diseases for the oral contraceptives.

While we agree with Dr. Camargo that, in a textbook way, case control studies are good for rare diseases, what we're talking about here is a risk that is low and a relative risk that would be relatively low. And the concern here is what in the trade is called either confounding by indication or residual confounding. Will they be able to get all the confounding out the way, theoretically, randomization should or will there be some confounding that will just linger?

A lot of the administrative databases, for example, don't have information on smoking status, which would be an important covariate, for example, in

pulmonary outcome.

So those are some of our concerns here with low odds ratios, the ability to take out all the confounding.

DR. SWENSON: Dr. Chowdhury?

DR. CHOWDHURY: I'm Dr. Chowdhury from the FDA. I just wanted to make one comment regarding the SMART trial and the SNS trial, which have been brought up here, and what we have heard from GSK, the difficulty in recruitment and the timeline that it took for them to conduct the SMART trial.

They do note that the SMART trial was a placebo-controlled trial done in the U.S. only, and the trial that we are talking about here, and we have heard the companies' presentations, in which they're talking about a global trial.

I wanted for the committee to hear perhaps from GSK what were the logistics of the SMART trial, which was an active control trial. It had almost a similar number of patients. And how long did it take for the SNS trial to be completed in the U.K.?

DR. JENKINS: While GSK is thinking about

that. Can I ask, Gerald, can you describe, also -- one of the issues, it seems to me, that's going to be very challenging both in the control setting and in the observational setting is the fact that the risk that we're looking for is an inherent risk of the disease.

So we're talking about asthma exacerbations, asthma-related hospitalizations, intubations, and death, and we're also trying to capture those as potential adverse consequences of the drug.

So how does that factor into the observational study paradigm? We've already heard it's very difficult to factor that into the control study paradigm. How does that factor into observational?

DR. DEL PAN: Right. So this is essentially confounding by indication. The event that may be drug related also could be disease related, and, I think as they showed on their slide yesterday, people with more severe asthma, who may be at greater risk for an asthma death, may also be getting more medications for asthma, such as long-acting beta-agonists, and that

relationship may confound the ability to tease that apart here.

So it's another one of the concerns we have about an observational study.

DR. KNOBIL: Kate Knobil, GSK. I don't have the exact enrollment figures for SNS, but I can tell you that it did enroll more quickly and it was in a single country, as well, region in the U.K.

The big difference about SNS was that it was not a safety study. It was an efficacy study. It was an experience trial to compare salmeterol as add-on therapy to four-times-daily albuterol. And there was no controversy, there was no specter of having to run a safety study.

So just to show you those numbers again from SMART, SMART, again, you're right, it was only run in the United States. These are the same numbers that I showed you earlier, just so you can see them. This is for Phase 2, not for Phase 1.

But, again, it was a study to look at severe asthma outcomes. In this case, the primary endpoint was respiratory-related outcomes, but still it was a

safety study and there was very little interest in the study, as you can see from these numbers.

So the context around these studies was different. So if you're studying a new medicine for asthma, people are very excited about it and they want to have more experience with it. When you put something in an informed consent which says, well, there may be risks, then there's a little bit less interest in participating, and I think that had an effect here.

DR. CAMARGO: Carlos Camargo, again, Mass General Hospital. I do want to raise this important point about confounding by severity. You heard it from several of the FDA staff and I tried to emphasize yesterday how critical it is.

But I want to make the point that it's not enough to just say bias or confounding. Think about the direction of that bias and confounding. So when I was first approached about this study design, my thought was, well, that's going to be hard to control for severity of asthma and the effect on the estimate would be to make the product look bad.

I reiterated this several times to GSK, because I said if we can't do this right, it will show your product to be dangerous when it's perhaps not. So it's very important, when thinking about confounding and bias, to think about the direction.

The issue here with unadjusted confounding is that the product will look dangerous when it's not, and I think that's a very important distinction and it will motivate GSK and anyone else who works on this who thinks that LABA are safe to try to optimally control for confounding by severity.

DR. BONUCCELLI: Cathy Bonuccelli, AstraZeneca. I just wanted to mention that the feasibility assessments that AstraZeneca did did assume recruitment outside of the U.S. The U.S. is the slowest to recruit. In our feasibility assessments, we have already made the assumption that half the patients would come from sites outside of the U.S.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: Thank you, Dr. Swenson. There were some issues that were briefly touched on

yesterday and, also, have been kind of mentioned in context today. But with the challenges of getting enough patients for a randomized control study, I was wondering what the sponsors were going to recommend in terms of what to do with the asymptomatic patient, where step-up therapy may not be warranted.

MR. PASCOE: Steve Pascoe, Novartis. As we said yesterday, we don't think it would be viable to persuade patients who are asymptomatic and well-controlled off LABAs to go onto a LABA. I think in the U.S., this is going to be especially difficult, given this whole conversation. So I think it's not an idea we should entertain.

DR. KNOBIL: Kate Knobil, GSK. This is exactly the conversation that we're having now about how are we going to select the population for these studies. And I think that we would have to ensure that patients were candidates for step-up therapy.

The other study design that you could potentially think about is stepping across. So if someone is well controlled on an inhaled corticosteroid, could you step across to an equivalent

does of the steroid in the trial? But stepping them up may be an issue. And these are the conversations that we would have to have before finalizing the protocols.

DR. ANDERSSON: Tomas Andersson, AstraZeneca. I agree with that, obviously. There are different ways it can be done. What we proposed yesterday is to include patients that would be candidates for treatment with Symbicort.

So it would mean that if you're on ICS and everything is fine, then you wouldn't change it. But, of course, that depends on how pragmatic you want to be in your design. We constantly hear we'll have tradeoffs of simplicity and perfection, so to speak. It would be hard in a large study to get everything perfect and getting relevant patients in will be the key point, of course.

DR. CARVALHO: Would you go just by subjective measures or would you use objective measures? Many times, patients actually subjectively may be asymptomatic, but objectively, their peak flows may be changing.

DR. ANDERSSON: The technical way we normally do it would be to have a run-in period with a defined treatment and, there, get a set baseline level so that we can define the patient.

That would, in a very large study, be extremely complicated and make it harder. A very pragmatic view would be to say it's up to the clinical judgment of the investigator to say what sort of patient is this, what medication does the patient need.

I think that's also something we should discuss, because it has to do with feasibility and what's possible to do.

DR. KNOBIL: Kate Knobil, GSK. I think you would definitely need both subjective and objective measures, just because patients are notorious at underestimating their asthma severity and the impact of their asthma symptoms, as we saw in the Asthma in America survey. So I think you'd have to have a mixture of both.

DR. SWENSON: Dr. Fink?

DR. FINK: A couple of general comments, one

of them being that in pediatric trials or adolescent trials, it would be very important to do Tanner staging, whether it was used as a randomization criteria or not.

There are marked hormonal effects of progesterone and testosterone on pediatric/young adult asthma and to ignore Tanner staging would really be to make it a poorly designed study, because an 11-year-old girl may be post-pubertal or you may have an 11-year-old male who is totally pre-pubertal. So Tanner staging, whether used as a randomization event, at least needs to be recorded.

I think it's also important to just comment on funding of safety studies is usually insufficient and that does affect recruitment in the United States. If these studies were funded at the same level of new drug trials, there would be much more rapid recruitment.

FDA could also participate in this; that if a randomized control trial is done using the composite endpoint, since hospitalizations and ER visits would be the endpoint, if the requirement to report all

those as serious adverse events were waived for this study, you would decrease the administration overhead and cost of the study dramatically, because in this study, there would be literally thousands of SAEs for investigators to have to file with their IRBs and with FDA.

That has been done, at least in one case, with a CF trial where hospitalizations, being part of the disease, were not considered SAEs. So how the trial is run by FDA, waiving the SAE reporting requirement for hospitalizations, if that was a primary outcome variable, would really lower the administrative overhead.

The other thing I think should be considered that I haven't heard discussed is the issue of withdrawal was raised this morning. The thought came to me that one of the answers to this that limits potential toxicity and exposure of patients to risk would be to design this as a crossover randomized controlled trial.

If there was a six-month crossover period, you would actually see the effect of LABA withdrawal

on half of the population that was on LABAs first and then withdrawn to ICS only. And a crossover trial would actually add some statistical significance, but numbers, but would also let you look at the LABA withdrawal issue and LABA addition in the other half of the population in terms of better control, and might be an idea design for an RCT.

DR. SWENSON: Mr. Mullins?

MR. MULLINS: Thank you. I wanted to move the discussion to a point that gave the committee some real world information on utilization, and I wanted to know from the sponsors -- because some of the dialogue I have and communication I've had with consumers is that they have had some issues with psychological effects and some impact from the combination therapies.

So I want to move this discussion toward addressing secondary endpoints. So I think we would benefit from any utilization data, such as discontinuation rate, that the sponsors might have and other information, real world information, because some of the suggested trial dosage that I've heard is

100 or 50, or 100, in that range of 100-150, 150-50. But in real world, some of the consumers tell me they're being prescribed 20-30 percent higher levels, dosage levels that are much higher than what I've heard proposed for the trial.

So I want the sponsor to address that, because I think we come out of this trial with irrelevant information that's not helping anyone.

Then my last question is for GSK. And I wanted to understand, just for clarification, did GSK agree to -- when they were not reaching -- in the SMART study, when you were not reaching your primary endpoint, did you agree to increase enrollment from 30,000 to 60,000?

So I wanted to clarify that and in the whole context of understanding observational versus a randomized trial. Thank you.

DR. KNOBIL: Kate Knobil, GSK. So before we started SMART and in the design phase, we had to estimate the rates of events that we would see, and that included asthma-related deaths and hospitalizations.

During the course of the study, the rates were much lower than we had anticipated. So, yes, in collaboration with the DSMB, we increased the target enrollment from 30,000 to 60,000.

The other question is just including a single dose in trials going forward, would that be applicable to many patients, was that your other question?

MR. MULLINS: Yes, it was.

DR. KNOBIL: So in the design proposal that we've put forward, we included all strengths. We would allow patients to come in at whatever strength that they were on or whatever strength was appropriate for their asthma. So it wouldn't be just restricted to the lowest strength of Advair. We'd have data on all of the strengths.

MR. MULLINS: That's what concerned me. I saw a very low dosage level and I know real world is much higher than that. So that's what concerned me.

DR. KNOBIL: Low dosage level where? I'm sorry.

MR. MULLINS: In the suggested proposed

trial levels that I heard. With some of the sponsors, I heard a dosage level that was lower than some of the dosage levels that I heard from consumers.

DR. KNOBIL: Well, in our proposal, the patient could be randomized and stratified to a dosage level that was appropriate for their level of asthma severity or asthma symptoms. So it's not limited to just a single dosage level. So I think it would answer your question of the applicability.

MR. MULLINS: Okay.

DR. BONUCCELLI: In the primary presentation, we did show some of the secondary endpoints that we have been thinking about, but I think that would be -- we'd be more than open to discussing what are the most meaningful secondary endpoints to capture.

So we talked about maybe number of oral steroid courses, what additional medications were needed, what asthma control measures, and, of course, safety capture. But we're open to other ideas about what people think is important.

With regard to the dose in the study, the

dose that we recommended for Symbicort is the most commonly used, most commonly prescribed dose. We did propose a single dose, but it was the one that we thought had the most relevance, because it's the most commonly used.

MR. MULLINS: I guess just carrying on with that. Do you have information on psychological assessments with adolescents or in pediatrics? That's my concern as far as -- do you see any indications as far as mood swings, anxiety, issues like that?

DR. BONUCCELLI: I'm not aware of anything of that nature. I will ask if anyone else has anything. I'm not aware of any safety signals in those areas.

DR. ANDERSSON: We don't have any safety signals in those areas for Symbicort versus ICS alone. In studies, what has been captured is asthma-related quality of life or quality of life measures. Now, to what extent that reflects psychological effects, it depends on how you define them.

Also, in controlled settings, we always see that the discontinuations -- when patients are in a

blinded study, discontinuations are higher for the ICS than for the combination treatment, because of lower effect.

MR. MULLINS: Do you have any information on discontinuation rates?

DR. ANDERSSON: I think in the overall dataset that we presented in 2008 here, I do believe that it was 12 versus 15 percent. That's overall, non-formoterol versus formoterol, and the discontinuations is higher if you don't get formoterol.

That, of course, reflects many things. It could reflect -- withdrawal can be side effects, lack of efficacy, many things. In this case, I think it mainly reflects lack of efficacy.

We talked about withdrawals yesterday when it comes to establishing effect and safety in a study and it's a major issue, because those patients that withdraw are usually not typical. They are usually more severe or have a -- they are those patients that you would want to retain in the study.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I have what I hope is a rhetorical question for the FDA and the sponsors. If we assume for a moment that there's a place for a randomized control trial for at least some of the outcomes that we're discussing, I've heard concern about competing trials, competing for subject populations, and I wonder whether there's another way to look at that.

It's possible, by having common designs and by having common outcomes, to go make some of those trials additive rather than competing, because if the outcomes are common, it's possible to plan a combined analysis or combined meta-analysis at the end of those trials. I'm wondering whether the FDA and the sponsors would be open to that sort of design.

DR. SWENSON: Perhaps we should have the FDA first and then we could have the sponsors.

DR. JENKINS: Yes. I can start. Obviously, you have to be aware, there are different devices that these drugs are delivered from. There's also the possibility that the different molecules could have different effects on this endpoint.

We saw the examples earlier of fenoterol versus albuterol. So you'd have to take into account all of those factors as you're thinking about how combinable would these studies be at the end of the day.

We did meet with all the sponsors together, I think, back in December. We can't, to my knowledge, force them to work together, but if they are able to, in some way, work together without violating the laws about being competitors or whatever, we would encourage that.

But I think there's a lot of factors that we would have to think about before you could really think about combining these studies in some sort of a LABA meta-analysis, because we really don't know that each molecule has the same impact.

We've even seen issues, as well, with the safety of different delivery devices. We've seen that with some of the agents in this class, as well as some of the anticholinergics. So even the delivery device can have an impact on some of the findings.

DR. D'ANGIO: I don't mean to imply that the

primary outcome should be calculated on the sample size of the three studies together. It's very possible that you're right that there will be effects in different directions or the different molecules will have different effects, and that it would, in the end, be impossible to combine some of these data. But if the studies aren't designed for the possibility of that, then that chance is lost.

DR. CHOWDHURY: I'm Dr. Chowdhury. Just to expand on the point that Dr. Jenkins just made, the issue of devices and the delivery characteristics on different devices, and, also, if these molecules -- we're talking about two long-acting beta-agonists are the same or not.

Going back to what Dr. Camargo said earlier, that we have seen that beta-agonists, some of the older ones, had negative outcomes, whereas albuterol actually did not. Control subjects with albuterol were absolutely negative.

So going forward, again, salmeterol and formoterol may, indeed, behave differently. We do not know that and randomized control trials with each of

them will probably address the question for each of them. But, again, combining studies, if they're similarly designed, is not entirely out of the question, and we have seen that being done for a lot of meta-analyses already.

Going to the devices, it is quite known that almost-same molecules given in different formulations, different devices, behave somewhat differently. Albuterol is one example and we have seen comparative studies when albuterol was reformulated from CFC to HFA-containing products, and the head-to-head trials are there in the product labels.

If you see the efficacy curves for them, they actually do not sprinkle (inaudible) on each other. They're actually somewhat different. And maybe here, we're talking about formoterol in two products. One is a single entity, which is a dry powder inhaler. Another one is an inhalation aerosol in a pressurized MDI, which is Symbicort. And the characteristics of the two may be quite different and there's no reason to assume that pharmacodynamically they're even the same.

Thank you.

DR. SWENSON: I guess you would have to turn back to the sponsors to see if they've given any thought to the ability to work together in some way, if there's a relatively common protocol you could possibly envision, that it's run by some third-party that's contracted by all of the sponsors, and there could even be stratification of the randomization by product or by center.

There are possibilities. I'm just wondering if the sponsors want to comment on whether they've thought about the ability to work together on these types of studies.

MR. PASCOE: Steve Pascoe from Novartis. I think, actually, this is a really critical issue, because I think we have to decide what questions we want to answer. And if we're struggling to answer the key question in one study aimed at, presumably, one molecule or class, if we subdivide it into three, that's going to become three times as hard.

I would suggest that we should look where the signal is coming from. Have we got a signal for

differential activity of these molecules or are we interested in the class?

I think both questions are potentially answerable, but just to be clear, the roadblock here is the external environment. So if we decide that a level of proof is needed for each question, to divide it up is a threefold greater burden.

In terms of would Novartis be willing to have a common thread through the protocols to make them additive, I think we would be actually enthusiastic for that approach.

The last thing I would say is that one of our concerns is multiplicity. And if we decide we're going to address three separate molecules or three separate drugs and one of them shows a signal, do we conclude that is a signal for that molecule or for the class?

I think if we project forward to ask that question, if the answer is we would conclude that is a signal for class, then we shouldn't initiate a program deciding to differentiate the molecules.

DR. BONUCCELLI: Cathy Bonuccelli,

AstraZeneca. We have been in dialogue with the other sponsors. I think, in our instance, we would like to do a study to specifically answer the question for Symbicort.

Beyond that, though, we have recognition that subpopulations within the study will be of particular interest. So we were aiming for a study that could be done similarly by all the sponsors, in particular, to sort of enable that subgroup analysis, if it was desired.

DR. KNOBIL: Kate Knobil, GSK. I would agree with the comments put forward before. I think a common thread would be a good goal. I think that, as you've heard today, all the sponsors have had a different proposal, and so I don't think we've specifically talked about working together.

But I do believe that we should have a robust answer for each of the molecules. So, again, a common thread is perfectly, I think, reasonable, but I think we do have to have appropriate studies for each of the medicines.

DR. SWENSON: Ms. Walden? No questions,

okay.

Dr. Fleming?

DR. FLEMING: I'd like to return to the general issues and expand maybe a bit on the FDA's response about issues around the strengths and weaknesses of observational studies against randomized trials.

Observational studies clearly have a role. They are particularly well suited to describe and understand natural history; to define what the event rates are, which is something we really need to understand as we plan randomized trials; to look at how interventions occur; and, to understand predictors, covariates; what predicts risk.

Basically, we're getting at associations. We're not getting at causality there. And we're talking about causality here. We need to understand causality. Observational studies are challenged in getting at causality, because as we've all talked about, issues around confounders, but it's more than that. It's issues around informative missingness; it's issues around not having ITT cohorts; it's issues

around having a well defined intervention group and a well defined control.

So where do they give us a sense about causality? It's been argued rare events. Yes, yes, rare events. So if you have an event rate that's 1 in 10,000 and it takes an odds ratio at least of 10, or a relative risk increase of at least 10, that's where you're going to be able to get causality insights.

I gave the example of Tysabri, where it should be 1 in 1,000,000 and it was 1 in 1,000, that's a 1,000-fold increase; or FDA, in their observational studies, in their pharmacovigilance plans, were able to show or identify that rotavirus vaccine had a more than tenfold increase in its inception.

Those are the kinds of settings where you're going to be able to get at this. ADHD drugs in children, there is a suspected potential risk in cardiovascular death, stroke, and MI, but at a baseline rate of less than 1 in 10,000, where a tenfold increase could be argued to be needed for that to offset the broad benefits that you get from symptom control.

So, in essence, yes, observational studies have a key role in hypothesis generation, in understanding natural history, in understanding covariates that are predictors, and, in the truest rare events, where it takes an odds ratio of 10 or more to be important, that's where their role would be.

If we look in this setting, just to point out why -- my argument -- that, as in other settings, getting at an odds ratio of 1.25 here is incredibly overwhelming if you are trying to do it with an observational study.

We've seen in the data that's been presented here for asthma-related deaths, the SMART trial indicated a rate, even though it was lower than we had expected, it was a rate of 12 per 10,000 person years.

The FDA meta-analysis is now saying it may be 3. GSK is putting forward data on Advair to say maybe it's even lower than that. In terms of asthma-related deaths-intubations, in SMART, it was 41 per 10,000 person years. The Salpeter analysis is saying 6.4. That's a sevenfold difference.

Why is that difference there? I don't know. It's a wide array of things that could be impacting that. It could be a differential use of ICS or other supportive interventions. There could be inherent differences in risk and seasonality and regionality.

If we're seeing, in our observational studies or our comparison of SMART versus other studies, differences of fourfold and sevenfold, how are you going to be able to, with an observational study, get a relative risk of 1.25? It has to be far greater. So if you care about odds ratios of 1.25 or even 2 or 3, then we need randomized trials.

And just very quickly, this isn't novel. We have encountered this issue repeatedly. I want to get into the specifics later on, but my sense is, in this setting, we can do what we need to do with 24,000 person years in adults and 9 to 18,000 person years in children. I believe we can get the answers we need with 24,000 person years in adults.

So just to put this into contrast, to talk about a couple of other settings. In Type II diabetes, following the July 1st and 2nd advisory

committee in 2008, it's been determined that it's no longer acceptable in this widely implemented setting to not understand safety and efficacy, and including rare safety, but critically important safety events, such as cardiovascular death, stroke, and MI.

Agents like muraglitazar and rosiglitazone had indicated excess risks, but we weren't sure what those true rates were, because we had only done small efficacy trials and had about 2,000 person years of follow-up.

So now, for every intervention in Type II diabetes, studies have to be done involving 36,000 person years. That's compared to what I'm arguing, I think we can do it here for 24,000 person years.

In the PRECISION trial, which is an OA/RA for COX-2 inhibitors, ongoing study there is involving 50,000 person years to understand celecoxib's effect on cardiovascular death, stroke, and MI against naproxen. Essentially, these are settings where one is trying to discern the difference between no increase and a relative risk of 1.33.

It this slowing the development of new

agents in Type II diabetes or in OA/RA? I don't believe so, because the efficacy studies that we need to do for approval in Type II diabetes, the efficacy studies still only involve 2,000 person years.

Plus, there's something that I always call the sense of urgency. One of the things I love about industry is that they get their eye on the target, they have a sense of urgency, and they get those studies done in an efficient and effective way pre-marketing, for those studies that are required for registration.

So I have no question about the fact that if these studies that we're talking about are implemented, that it will not stand in the way of the development of new interventions for asthma, as they are proposed.

I've been on the data monitoring committee for SMART. That did, in fact, enroll 26,000 people. I'm chairing the data monitoring committee for PRECISION, which is 20,000 people. I served on the ziprasidone data monitoring committee, which was looking at ruling out excess risks because of QTC

effects of ziprasidone, that entered 30,000 people.

We've done these trials. Yes, they're a challenge, but they're doable. I admit, the sense of urgency is less for sponsors in these settings that have led to somewhat longer periods to conduct these trials, but they certainly don't prevent the ongoing conduct of other trials that are being done for efficacy.

One other quick example, Women's Health Initiative, large-scale clinical trial. And I'm proposing we could proceed here with 24,000 person years. The Women's Health Initiative had over 200,000 person years, looking at the effects of vitamins, hormones, and diet on cardiovascular risk, cancer risk, and osteoporosis.

Observational studies, extensive observational studies had indicated the favorable effects of hormone use on cardiovascular risk in women. The Women's Health Initiative indicated that the relationship is the opposite; they aren't, in fact, beneficial, as observational studies had shown. The large randomized trial had indicated that there

was harm.

So we don't always get -- we get clues, useful clues in observational studies. We don't always get the reliable answers that we really need to understand.

I would argue, kudos to GSK and to the FDA for SMART, 14,000 person years and extremely important insight about what is the effect of LABAs when you're using it with variable ICS. It's the best information we have in that 14,000 person years.

One last comment, and, that is, if we do an observational study, we're going to overestimate risk. Well, by the way, I don't know whether that's a good thing. Why is it a useful thing to indicate risk that doesn't exist? But, again, I'm not sure it's going to overestimate risk necessarily, because there are clear issues of informative missingness.

If we do a randomized trial, we have to make sure we're following all people's outcome. We need an ITT cohort, for all the reasons that we understand, to avoid bias from informative missingness.

You're not able to control that type of bias

when you have an observational study. You need a well defined -- for a safety trial, it's a higher bar even than an efficacy trial for interpretation. You're trying to rule out excess risk.

An efficacy superiority trial, if there is irregularities in how the study is conducted, if there's informative missingness, if there's lack of adherence to the experimental, if there's cross-ins, and you show a difference, you say, ah, thwart CRA, there would be a difference even more so if I had done it in a pristine way.

This is not inferiority. If there are any kinds of these noises going on with informative missingness, if there's lack of clear adherence to the intervention, if the controls are getting LABA or other interventions that could be harmful, that's going to dilute out the difference.

So if we're reassured that we're not seeing anything, do we have assay sensitivity in the data that we're looking at to determine whether there's an effect?

So it is not true to argue that if you do an

observational study, you're going to get an overestimate. You may have lack of sensitivity to true risks that exist.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: I agree with Dr. Fleming on the issue of observational versus random. I want to take the randomized control trial in a little bit of a different direction.

It seems that the fundamental disagreement between the FDA and both the sponsors and the professional societies is what happens when you withdraw the LABA. Do you need to withdraw it earlier or is it safe to keep going?

There doesn't seem to be disagreement of who should get on it, only those with the worst severity, where the steroids are not doing the job. I would submit that maybe a way to go around this, and maybe this follows Dr. Fink's suggestion a little bit, is a randomized withdrawal study; get everybody on who you would have gotten on, who all now physicians are now prescribing LABA, and, in a randomized way, withdraw or not withdraw them from LABA after a certain period

or after they hit control, and then see do you have a different safety signal or don't you have a safety signal when you approach it that way.

That might answer the question directly of that third bullet on February 18th that is causing so much controversy in these last 24 hours.

DR. SWENSON: Does the FDA have any comment to that? Okay. Dr. Wolfe?

DR. WOLFE: I raised this issue yesterday and it was the issue of equipoise, actual via the IRB or perceived by doctors and patients, and it was not meant to deter the very good discussion that has happened and will continue to happen on the trial.

It's not as though if you decide there's not equipoise, you shouldn't bother discussing trials. It's not why it was raised. It clearly has an impact. I mean, I don't think you can do statistics, but I think there's a statistically significant interaction between the discussion, perception, et cetera, of whether we're at equipoise and the ability to design and, particularly, recruit people to a clinical trial.

There's no question in the comments made,

after I and others raised this issue, that companies said that given what the new labeling is, namely, you stay on a LABA as short as possible once you've been stabilized, that is, in fact, inconsistent with the trial.

Now, Dr. Jenkins and others this morning have said that that will be written in such a way as to not explicitly preclude participation in a trial, and I think that probably could be done.

But I want to go back to this third option between observational and one randomized control trial, which is a meta-analysis. Many of the kinds of information we have learned about rare events came, and, to the extent that it is a collection of studies meant to look at causality, came from meta-analyses, where, in and of themselves, there weren't enough rare events.

Again, the second part of the Salpeter paper, I would like to hear a discussion from Dr. Mosholder, from Dr. Fleming, or anyone else who's had a chance to look at this paper. It was sent out in the last few weeks.

In the part of the paper that is looking at just those people who were on concomitant corticosteroids, in six of the trials, there were no intubations or deaths in the corticosteroid group in each of those; there was one in the beta-agonist group. And in the Glaxo data, it was eight in the beta-agonist and three.

Now, that's not a study that says you prevent intubations and deaths by using these drugs. It suggests, small numbers and everything, that there may be an increase.

So I would like to hear more of a discussion about that, because it's clearly one of the elements other than the FDA's labeling changes that would make people wonder about participating in the trial.

I completely agree with Dr. Rosebraugh's comment, and others, that when you're talking about a new drug, there isn't that much difficulty recruiting patients, because the new drug trials are, in fact, at equipoise. They are not done primarily as safety trials. They're done as efficacy trials and whatever is known about the risks from preclinical or whatever

is mentioned, but I think that the ability to recruit to those studies is much more than the ability to recruit to other studies, where explicitly it's done primarily as a safety study and it's predicated on an inclination by the FDA to tighten up the label, because of concerns about risks, not about benefits of the drug in terms of intubations and death.

So, please, more discussion from Dr. Mosholder. We heard the industry's efforts to try and attack the Salpeter study and that was the last thing we heard.

So, Dr. Mosholder, Dr. Fleming, and anyone else who's had a chance to look at this study, please. Thank you.

DR. MOSHOLDER: Andy Mosholder, FDA. Just a couple of points to follow-up on that. The Salpeter paper -- and I should say, I guess, that these are my own opinions. We've heard from my managers that CDER has already decided that we're at equipoise on this issue. So it's worth repeating these are just are my personal views of the data.

If you look at the Salpeter, the forest

plot, the point, to me -- section number 1 are the trials that we know pretty well by now, where use of ICS was variable and not specified.

The second section was the trials where the patients all received corticosteroid of some type or another. And the point is if you look at them just sort of visually, you don't see that there's a dramatic difference in the trend of the data, whether corticosteroids were sort of used variably or always. So that sort of raises the issue of whether the corticosteroids really impact the directionality of the risk.

I guess the second point, Dr. Sears raised yesterday that the imbalance in the section 2 where all the patients received corticosteroids could have been due to under-dosing of the steroid in the LABA arms versus the higher dose in the corticosteroid arms. I mean, that's a good consideration.

I'm not sure that helps get you back to equipoise, though, because, actually, one of the designs under consideration would be LABA plus ICS versus a higher dose of ICS, and these data would be

speaking to the greater safety of the higher ICS strategy.

So those would be my comments.

DR. SWENSON: Dr. Hubbard?

DR. HUBBARD: Richard Hubbard. Yes. Thank you. First of all, I know that the labeling discussion is not one that we're going to focus on today, but I would like to acknowledge and, I guess, appreciate the words of the FDA and Dr. Jenkins earlier that much of what has been said about labeling is still open for discussion, that the final wording certainly has not been released.

In light of what we've heard from the public, as well as concerns, I'm sure, from the sponsors, that we'd welcome a chance to have further discussions about labeling.

Second of all, I do feel honor bound, as a representative of industry, to note that there are significant opportunity costs that are not being appreciated by doing large trials like this, certainly, from three sponsors doing large trials.

I'm not going to put a dollar figure,

because I don't have one, but it will be very large. And that we may be forced to decide whether to do additional asthma studies that we might want to do or in other therapeutic areas that would be sacrificed by having to commit a lot of money to do this, which is not to say that we don't take safety very, very to heart as something that we do need to evaluate. But having to do significantly large trials where there might be other more efficient alternatives to get to the same question is one that we really should think about.

Now, I think the FDA and others have mentioned that with these trials, they're likely to be global and I think you have to understand what a global trial means. It doesn't just mean we're going to go to Canada and Australia and New Zealand.

Global trials, in all indications and in all diseases now are done substantially -- a lot of patients are enrolled from India, China, and Eastern Europe, and that has to be factored into how do you want to interpret whatever results are going to come out in six or seven years when these trials are going

to be done.

Finally, as a final point, I'd just like to encourage members not to start adding too many additional factors into whatever trial is done, such as multiple secondary endpoints, crossover designs, too many efficacy assessments, inclusion of lots of biomarkers, for instance.

All those things are certainly very important to understanding asthma, but they will only greatly complicate whatever trial is likely to be done in terms of enrollment, duration of whatever it is to get the trial done, recruitment of investigators. They have to have certain capabilities that might not be necessary in a large, simple trial.

So just to keep in mind that while we certainly want to do our part to cooperate to get the safety information in whatever the best manner and most efficient manner is, that we do keep in mind that this is going to be a significant burden on everyone involved.

DR. SWENSON: Dr. Knobil?

DR. KNOBIL: Kate Knobil, GSK. I just

wanted to clarify a little bit about the Salpeter paper. I know we've talked a lot about it and I don't really want to dwell on it too much, but just to clarify the use of inhaled corticosteroids and what the data actually are and what we showed back in 2008.

There's a difference when patients report that they're taking an inhaled corticosteroid that's prescribed by someone else at baseline versus them taking it as a study drug in a medication trial.

We have had two events in patients taking inhaled corticosteroids in a monitored way in a clinical trial, one with salmeterol plus BDP and one with salmeterol plus FP, and that's it. That's all we have. The rest of the events, and I can't separate them out in the tables in Salpeter, are all background, at least in the case of the salmeterol.

Yesterday, Dr. Mosholder showed the meta-analysis from Weatherall that showed only those studies that included ICS and salmeterol in separate inhalers. The next table in that paper, which I'd like to show you now -- and that's the bottom table.

So Dr. Mosholder showed table 4 yesterday.

If we look at the data from the patients who were taking salmeterol plus FP in a fixed dose combination inhaler, or Advair, there were no asthma-related deaths, there were four all-cause deaths, and there was no increase hospitalizations.

So I think that when we take these data into account, we should look at all of the data that are available, not just the earlier data when salmeterol was used very early on in its life cycle, when the use of inhaled corticosteroids may not have been as well established.

DR. SWENSON: Dr. Joad?

DR. JOAD: Yes. This is actually a follow-up to that comment. I would like to suggest that the studies include some sort of dosimeter or something to show that a dose has actually been taken, because I think a number of us believe that part of the success of a drug like Advair or Symbicort is the fixed combination and that you don't get the benefit of the LABA experience without also getting the inhaled steroid.

I know in the recommendations from the FDA,

they went with that concept for children, but not for adults. So we sort of have a not perfect, but a chance to compare the formoterol in the Symbicort with the formoterol separate from the inhaled corticosteroid.

If they do show differences, it would be very useful to go back and see were the ones that were getting formoterol not in a fixed combination really getting the same amount of steroid as the ones that were getting formoterol with the inhaled corticosteroid as a single device.

So I don't want to add a lot, but I think that would be an important thing to do. And that, of course, would be the best scenario, because it's a clinical trial. You know in the real world, it would be a lot worse than that as far as any adherence.

DR. SWENSON: Dr. Brittain?

DR. BRITTAIN: I guess I want to, first of all, echo how strongly I feel that it is important, if at all possible, to do the death-intubation endpoint and if that means pooling the studies to get the 20 or 25,000, I think that that's something that should be

done.

But I also have another concern that these would be non-inferiority trials, which is the right design. But it might be helpful -- I remember GSK yesterday mentioned a superiority analysis that could be done in the context of the non-inferiority design, which would help maybe prove that they have assay sensitivity or difference-detecting ability.

So I wanted to know if you could talk about that, whether you could do -- if I remember correctly, it was sort of like the FDA composite endpoint, plus exacerbation, that you thought you would have a superiority. Is that right?

DR. KNOBIL: No, actually. You can show the slide.

So the sample size estimates and the feasibility on the composite endpoint were done on a non-inferiority design for asthma-related death, intubations, and hospitalizations. The superiority design was done on our proposal for a study to compare Advair to FP in exacerbations requiring oral corticosteroids. And the reason that we chose a

superiority design is that in the meta-analysis that I showed at the beginning of the presentation, there was a significant benefit, albeit when we pooled all of our studies together. And we've shown, in individual studies, numerical decreases or sometimes statistically significant decreases in smaller studies.

So this would be an adequately powered study, but based on our previous data, we feel that it would be better designed as a superiority study based on the data that we already have.

DR. BRITTAIN: But even in the design we're talking about, the randomized study, where the primary analysis would be the safety non-inferiority analysis, it sounds like you could do a superiority analysis in the same study, where you would combine, I would think, perhaps combine all the endpoints so that you're including -- maybe I'm misunderstanding.

But could you have a composite plus exacerbation and get superiority?

DR. KNOBIL: I'm guessing that you could, if you said that a priori. I'm not a statistician. So

when we design a trial for a non-inferiority design, it usually has a different sample size, and you would know better than I would. I don't know.

DR. BRITTAIN: I'm saying it just be another analysis within the non-inferiority design that we're talking about.

DR. KNOBIL: I think if we designed that a priori, it's something that we could potentially do.

DR. BRITTAIN: I think that might help address the risk-benefit in a more direct way.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: Thank you. This is probably going to be just a quick question. I had complete faith in death as an outcome until the discussion yesterday, when a patient who came into the hospital with asthma and was intubated because of asthma died because of sepsis and didn't have an asthma-related death.

So I'm wondering whether there are ways to expand our definition or to create a more inclusive definition of causes of death that would improve the power of any of the trials that are being discussed

today.

DR. SWENSON: Anybody wish to comment? All right. Dr. Fleming?

DR. FLEMING: In general, I'm very supportive of an idea of being more inclusive. Cause-specific events are problematic, because it's not always obvious whether the death was due to the specific cause that you are trying to pursue.

So being able to look at an all-cause outcome has a certain level of greater interpretability, and it does give you more events. When we looked at all-cause mortality -- I don't have it on my fingertips -- in SMART, there were probably twice as many events.

The issue, though, here is if one is if one is doing non-inferiority, if one is ruling out an unacceptable increase in risk and you do have a fairly effective way to identify what are, in this case, asthma-related deaths and it's that mechanism that we think we are impacting and we're not impacting other causes of death, then you're diluting your overall sense, your signal. You're actually getting things to

look more similar and you're losing sensitivity to a true effect that's unfavorable on the specific cause of interest, which is asthma-related death.

So the bottom line is in a non-inferiority trial, if we dilute the endpoint with many other kinds of events that are, in fact, unrelated, we reduce our sensitivity to being able to detect what would be, in fact, an unacceptable adverse effect on a specific cause.

So I would say the same thing for all-cause hospitalization. If we just looked at all-cause hospitalization rather than asthma-related hospitalization, we'd get a whole lot more events. In a superiority trial, if you can show superiority, I'm really happy. But in a non-inferiority trial, if you fail to show a difference, you're diluting away the signal.

Just one last example of this. Many have very effectively pointed out that if you only looked at the combined endpoint of asthma-related death, intubation, and hospitalization in SMART, you might not have seen the concern, because it's far more

apparent in the more serious events.

So you're diluting away your ability to see what it is that you most care about.

DR. ROSENTHAL: Just a quick follow-up. I think that maybe the answer lies somewhere in between the two extremes, then, because I think, intuitively, most people would say that if a patient is admitted to the hospital with asthma and dies of a nosocomial infection, then in some way, that's an asthma-related death. If a child who's using any kind of beta-agonist comes into the hospital with a malignant arrhythmia, one has to at least ask the question of whether the beta-agonist wasn't related.

So all I'm suggesting is that there probably is a gray zone where we can improve our power and keep it relevant.

DR. MOUTON: But if you think death is subjective, you should try intubation or hospitalization. Regis McFadden analyzed intubation and showed that there were absolutely no objective criteria used for making that decision. And the hospitalization trends are driven by insurance status.

We've seen hospitals in Atlanta where the admission rate for children went down threefold with a change in insurance status in the town.

DR. FLEMING: Could I, just one, to endorse what Dr. Rosenthal just said?

DR. SWENSON: All right.

DR. FLEMING: I agree with you, Dr. Rosenthal, that it is important, if we were to go with a cause-specific, to have that be sufficiently comprehensive to capture unintended off-target effects on the outcome.

So a classic example is mammography in women in their 40s for breast cancer. If we look at all-cause mortality, we're going to dilute away the ability to find out whether these are effective in reducing breast cancer-related deaths. But if these interventions increase suicide to a level that the overall net effect on mortality is neutral, then we would have made a mistake to look only at breast cancer-related deaths.

So you're absolutely right. If we do use cause-specific, technically, that cause-specific

should be capturing events that are not only the disease targeted events we're trying to prevent, but off-target effects the intervention may have, and that's, obviously, hard to know what those are. So at a minimum, we should be having supportive analyses that are more inclusive, looking at totality of events.

DR. SWENSON: Dr. Ownby?

DR. OWNBY: I'm surprised, in this discussion, we haven't talked about another endpoint that I think is somewhere in between, and that is admission to intensive care unit. I would argue that -- and we could have a long discussion. I appreciate what Dr. Platts-Mills says, that a lot of these decisions that physicians make are somewhat capricious and not always on a clear set of guidelines.

But on the other hand, that is when hospitalizations become very risky. Obviously, intubations are almost always a subset of that group and it would increase our power, but I think still get at the question of who is really critically ill with

asthma as compared to the more usual admissions that are not so risky.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: I still want to ask a question. I sort of think about this case control study. One of the problems, it seems to me, one of the other issues about a case control study has to do with, actually, estimates of absolute risk.

See, I think that even if this either clinical trial or case control study comes out with increased risk for LABAs, they're not going to be taken off the market. I think that if they were going to be taken off the market, they would have been taken off the market after the previous trial.

The opinion in the medical community -- as a statistician, I approach this, I don't even know whether something is useful. I come at it just sort of blind. But the opinion of the medical community that was given at the last three meetings was that these drugs are very, very important in the armamentarium of doctors, that they didn't want to give them up; and, unless something else comes along

that seems to be better, that's going to be a continued feeling.

So I don't think that we're going to -- even if these trials are sort of negative, that these drugs are going to be taken off the market. And given that, it seems to me the most important thing is going to be the point estimate of the absolute risk.

What I was hoping people are doing now, I have no idea whether they're doing it, is, well, you know, we have this other drug for you -- in other words, when the patient comes in, having seen the TV ad about Advair, to the doctor, the doctor should say -- I'm hoping the doctor is saying to the patient, "Well, they're very good drugs. They do have a good effect on most of my patients, but there is a risk, which," since I have now read the Salpeter article, "is maybe 1 in 1,500, maybe, of increasing the risk of having a catastrophic event, which I don't like to mention to you, because you have it anyway. And so what do you want to do?"

[Laughter.]

DR. SCHOENFELD: I don't know that this --

this may never happen. This may be only in the way doctors speak to statisticians.

[Laughter.]

DR. SCHOENFELD: But in any case, if the doctor doesn't say this to the patient, at least the doctor goes through it, in his mind -- hopefully, the doctor goes through it, in his mind. And what we're trying to do is refine this information so that the doctor will have this and say, "Well, it's really not 1 in -- maybe it's 1 in 5,000." We might do this big clinical trial and there might be no deaths at all, in which case it's less than 1 in 5,000. It's fairly rare, and so they won't have to worry about it that much.

So I think that's the main advantage of a trial. But what I worry about in a case control study, and maybe Dr. Camargo can discuss this, is how do you get any measure of the absolute risk in a case control study.

DR. CAMARGO: Carlos Camargo, Mass General Hospital. The short answer to your question, I agree with what you've just said. I think this absolute

risk is going to be vanishingly small. It may not even be there. That is a possibility we have to always keep in mind with equipoise.

So I think the advantage of an observational study would be to assess the relative risk, and that has some value when taken into the context of populations, which, again, this observational design would deal with the populations.

I do want to respond to a series of comments about observational epidemiology and remind you that I am a card-carrying member of the clinical trial community, with experience in single-center trials, multicenter trials, multinational trials; standing member of the NHLBI Clinical Trials Review Section. I love trials.

[Laughter.]

DR. CAMARGO: But in these settings, I often hear some subtle and not so subtle put-downs of observational epidemiology. And we did hear in this meeting today that an odds ratio, a relative risk of 10, now, that would be believable. And then that slipped to 5, because it did seem a little extreme,

which just happens to be a little bit over 4.

Then we heard the traditional trot-out of the Women's Health Initiative, and we could spend -- you think this is complicated. We could spend days talking about the differences between a beautifully designed and conducted randomized trial and the inferences that can be made from that trial and whether or not they're relevant to a woman starting to go through menopause who starts to take estrogen. There's papers and events and theses around this.

But let's return to this issue about the magnitude. There are many, many more studies than the Women's Health Initiative from epidemiology and compared to a trial that show things that are true.

Dr. Fleming correctly directed our attention, for instance, to diabetes and in the context of heart disease. And I would just remind you, there are no randomized trials assigning people to diabetes or not diabetes, and those studies, observational, with all their flaws, suggested relative risks of 1.5 to maybe 3.

Likewise, smoking and its association with

heart attacks and strokes has relative risks of about 2 to 3. These are accepted as true, as causal. And I would submit to you that having a standard of 10 or even 5 is excessive.

DR. SWENSON: Okay. At this point, we should take a break. It's now roughly 10:30. We should be back at 10:45.

[Whereupon, a recess was taken.]

DR. SWENSON: At this point, we'll now turn to the specific questions that the FDA has asked us to address in the design and consideration of critical elements of the proposed study.

We'll try to keep to a timetable that I'd like to finish by about 2:30 or so. There are some that wish to get planes out at a reasonable point in the late afternoon or early evening. I hope this won't diminish the discussion too much. We'll just see how it goes.

Again, at this point, I have to remind you that this portion is open to public observers and public attendees, but they may not participate, except at the specific request of the panel.

So I'd ask Kristine Khuc here if we could pose the first question here. And this, as you see, will be exactly verbatim the question in number 2, except that it'll be toward the pediatric question and how to design a study for that.

So I'll read here that "The study endpoint to be considered here is the composite of safety endpoint of asthma-related hospitalizations, asthma-related intubations, and asthma-related death being proposed for this study." And the discussion should center around the adequacy of this primary endpoint to address the safety concerns of LABAs for the treatment in asthma, and then to look down at the level of risk for LABAs that would be considered acceptable to rule out a risk.

What would be the acceptable upper bound of the 95 percent confidence interval? And then any alternative endpoints that could be considered to evaluate the safety of LABAs for the treatment of asthma in adolescents and adults.

So with that, I know that we have questions that were still remaining from the previous portion.

I hope that for those of you that didn't have a chance, that you'll have a chance in these particular questions to raise that.

But perhaps we should go to the discussion point of A and hear opinions about the adequacy of this primary endpoint for the purposes of this study.

Dr. D'Angio?

DR. D'ANGIO: Sorry, didn't mean to jump in front of Dr. Wolfe there. I think that we've heard a fair amount of discussion around the fact that this endpoint would be driven by hospitalizations, which may not be a reasonable surrogate for death and intubation, and that we may need to think about whether we need to separate out the very severe outcomes from the merely severe outcomes.

I'd like to second Dr. Ownby's suggestion that we consider ICU admissions. I'm not an asthma clinician, so I don't know whether that's a reasonable surrogate, but I think it's worth discussing. And I don't know how easy it would be to obtain those data, although I suspect it would be as easy or as difficult as it would be to obtain hospitalization or death.

So I think that those are my comments.

DR. SWENSON: So we have this idea raised about an ICU admission as being some point intermediate between a hospitalization as an adverse event and then the clearly unequivocal severe events of intubation and death.

Dr. Wolfe, I think you were next.

DR. WOLFE: The point was made by Dr. Fleming earlier that had the primary outcome for the SMART analysis included hospitalizations, for the reasons that we just heard, it would have been swamped out by the hospitalizations.

In that meta-analysis, in one group, it was even. It was not advantage-LABA. And in the other group, it was actually worse in the LABA group. But aside from that, no one is saying you shouldn't look at hospitalizations.

But I think that focusing the primary outcome on intubations and deaths and possibly, as Dr. Rosenthal suggested, having a reasonable, not out of control, a reasonable expanded definition of death; so that, for example, the person who wound up in the

hospital because of an intubation and then got sepsis, that is, arguably, a death related to the asthma or the treatment, whatever.

So I think that it's important to stick with the more severe, worrisome, more likely to yield the answer to the concerns. The concerns that we all have were originally driven by SMART, although that was when it was single-acting agent and the result of that is we strongly oppose the idea of anyone using one of these agents by itself anymore.

Now, at the next level, our concerns are driven by deaths and intubations, primarily, and I would strongly advocate that we stick with that as an outcome, possibly considering ICU. But as was pointed out by Dr. Fink earlier, you have to sort of factor in places that have ICUs, don't have ICUs, because if your trial is done in location A versus location B, the ICU existence or the nature of it or the busyness of it may confound it.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: Can we absolutely clear that we're not talking about LABAs, we're talking

about combination? This is here written as LABA. We're not discussing LABA on its own.

DR. SWENSON: I would think it's the LABAs in combination with ICS versus ICS and the risks that the LABAs added on to ICS represent.

DR. CHOWDHURY: Just to make it clear that we have laid out the hypothesis that you just discussed extensively and the trial arms are LABA plus ICS versus ICS.

DR. PLATTS-MILLS: Right. And that actually means LABA plus ICS in a single delivery device.

DR. CHOWDHURY: Again, that's something which will come up later on, but generally, with the concept that I was laying out the other day, it will depend on the product. For example, for salmeterol, you have that. For formoterol, for one company, you do, which is Symbicort. For the other company, you do not. So it can be either.

DR. PLATTS-MILLS: Then the outcome, if the outcome we're really interested in is death, I would submit that the data we already have says that we cannot address that at all in a controlled trial,

because the size of the controlled trial is much too large, we can't do that. The other is very subjective and there's a lot of evidence that we wouldn't get an outcome.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: Thank you. For the study endpoints, one of the things that comes to mind is the time of presentation for a patient many times dictates whether the patient lands in intensive care, is endotracheally intubated or managed with noninvasive ventilation.

Many times, these patients can come to us, we can intervene quickly and turn them around -- the nature of asthma. I would wonder about other endpoints. And I agree with the panelists in terms of the more severe outcomes, such as an intensive care admission, but just limiting it to endotracheal intubation may be not quite right. We may need to split it apart between an actual intubation and mechanical ventilation versus management with BiPAP or something along that line.

DR. SWENSON: Dr. Morrato?

DR. MORRATO: I just wanted to echo the previous points being made about really focusing on how you clinically translate what we're trying to look at, which is risk of serious exacerbation and how do you translate with hospitalization.

The piece I'd just like to add is that this is particularly important if you're looking at sites not just within the United States, but as some have proposed, half of the sites occurring outside of the U.S.

So as that endpoint gets decided as to what's clinically relevant, as to if there's a level of hospitalization or characterization of hospitalization, it really needs to be in context of where is the study going to be conducted. And that may actually inform which sites you shouldn't be including from these other countries, if the health care system is just too disparate in order to have a common definition or a common clinical approach across geographies.

I just wanted to add that.

DR. SWENSON: Dr. Redlich?

DR. REDLICH: I just wanted to add a comment about -- and this has been addressed already -- randomized control trials and observational studies. I realize that there is a common belief that the randomized control trial is at the top of the hierarchy and will come up with a definitive answer. But that's not a universal belief, and there are serious flaws with randomized control trials.

The way these questions are structured are all assuming how to fine-tune a randomized control trial. It seems to me there's a more fundamental question, which is, is that an appropriate study to be done to answer the question at hand. And I have never had an asthmatic patient ever who has participated in a study, even if they wanted to. They're not eligible, not able.

So a trial may answer -- if you're lucky, it may answer a question. It may not answer a question that has any practical or clinical relevance.

So I have trouble with these questions, because I think there's a more fundamental question, which is, should we be doing a randomized control

trial to answer the question.

My understanding is the question of concern, based on all the past literature, is, is there an increased risk of death. The prior literature, from my understanding, does not suggest that there's an increased risk of these other outcomes related to long-acting beta-agonists with the steroids. But we're suggesting other outcomes to get enough of a sample size. But to me, there's a more fundamental question. Even if it was feasible, would this be a study that would be useful to do?

DR. SWENSON: Perhaps just the FDA could answer this question about whether what we're really discussing within this question is a randomized control trial or is it broader than that?

DR. ROSEBRAUGH: Well, I think when we originally wrote the questions, we were anticipating it would be in response to a randomized trial. But I think if folks want to open up the issue of whether it should be a randomized trial or not, we would be interested to hear that dialogue.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: (Off microphone.)

DR. SWENSON: All right.

DR. CNAAN: Sorry. My comment was made regarding the different worldwide standards and we have to come up with something that is very simplistic and severe regarding intensive care.

DR. SWENSON: That was Dr. Morrato's advice.

DR. CNAAN: Yes.

DR. SWENSON: Okay. Dr. Krishnan?

DR. KRISHNAN: Great. Thank you. I have two comments to make, one along the lines of endpoints. Death and intubation are essentially variants of respiratory failure and there's increasing use of noninvasive ventilation for patients with respiratory failure, and, as pointed out by Dr. Carvalho, in some cases, we're able to avoid intubation because of early aggressive management.

So from the standpoint of endpoints, I would say that it would make sense to me, it's logical, as a physician who takes care of patients both inside and outside the ICU, that if we're going to talk about endpoints, it should include death, intubation, which

is basically invasive mechanical ventilation, and noninvasive mechanical ventilation as a composite.

The ICU addition also is attractive to me, because it's all about early aggressive management and the avoidance of those complications. So I think my suggestion would be death, intubation, noninvasive ventilation, and ICU admissions.

Now, on a separate topic, which is what study design is appropriate, because as you pick these respiratory failure endpoints, they become rarer and rarer, although I've just provided some ways to broaden and perhaps calculate a few more events, I remain concerned about headlong pursuing a randomized clinical trial. We've heard about, of course, the various limitations that are written in textbooks and review papers about limitations. Those are well known when using observational study designs.

I'd like to echo a comment that was just made here about how hard it is to enroll patients into a clinical trial. I can tell you, as a pulmonologist and as a researcher trying to enroll patients, this is going to be a really tough study to convince somebody

to want to join a safety study.

Essentially, what we're going to say is "We think it might cause death or respiratory failure; we'd like to know if you'd like to enroll in this study to determine if it causes death or respiratory failure." That's going to be one heck of a hard sell.

Moreover, along those lines, even if you get past that, the issue is how do you design the study and, along those lines, I was thinking there are two types of patients you might want to enroll. One is an asymptomatic patient who is already on inhaled steroids, and that patient would be very hard to sell that now I want to add a medication that could be injurious and I want to know if it's injurious. I think that's a nonstarter.

The other possibility, of course, is to take an asymptomatic patient who is on combination therapy and tell them, "I'd like to determine if peeling off the long-acting beta2-agonist is worthwhile," and, again, I can tell you, as a clinician, that's a very hard sell for someone who you have gotten under control to now say I want to take off a drug.

Others may feel free to disagree with me, but that would be a difficult sell. I've actually sent the proposed labeling changes. I've had the opportunity to talk with patients about it and it's a tough one to enroll people who would be willing to be at risk for getting rid of the LABA, given all the data about the effects of withdrawal.

So I guess what I'm saying is enrolling asymptomatic patients in a clinical trial is going to be a really tough uphill challenge.

The other possibility, of course, is to take a symptomatic patient and to enroll them in this clinical trial, if, ultimately, that's what we propose. And there, too, I think it's complicated, because if you take someone who's symptomatic on monotherapy with inhaled steroids, then your option would be to randomize them to the same dose of inhaled steroids plus LABA or a higher dose of inhaled steroids as your alternate.

That's complicated, because now you're comparing two different doses of inhaled steroids and we don't quite know what inference you could make

about safety, because it might have to do with dose of inhaled steroids mixed in there.

The other option, of course, is to take a symptomatic patient on whatever dose of inhaled steroids they're on, randomize them to addition of LABA or they continue the same dose of inhaled steroid on which they were symptomatic. That would suffer some ethical issues, because a patient is telling you "I can't breathe" and you can't imagine just leaving them on whatever therapy they were already on.

So no matter which way I try to slice this, I have concerns about a randomized clinical trial. And I, too, like was mentioned by other speakers, like clinical trials. I have participated in clinical trials. I review clinical trials. I like them. But this particular case, it's problematic not only from the various reasons we've talked about, but literally on the ground recruiting for such a study, it's going to be a tough one.

DR. SWENSON: Dr. Joad?

DR. JOAD: I think everything I was thinking has been stated. Thank you.

DR. SWENSON: Then, Dr. Fink?

DR. FINK: In thinking about this question, I think it occurs to me that even death in asthma is not absolute. And we like to think of it as an absolute, but if you actually look at the studies on asthma deaths, in the United States, about half the asthma deaths occur in hospitals.

So that issues like access to the hospital, your risk of death is higher if you live an hour away from a hospital than if you live five minutes away. That hour away from a hospital doesn't have to be geographic. That can be an inner city family with a poor EMT response time.

Until we better understand asthma deaths -- if you move to Australia, 90 percent of deaths occur outside of the hospital. If they participate in the study, there isn't even equivalency of death as an outcome measure for asthma.

So my takeaway point would be whatever endpoint we choose is arbitrary and I would almost go for prolonged emergency room visits and hospitalizations, because they are the major driver of

cost. And if there is a significant increase in those in LABAs, then that is a real concern to the health care system. If there is no increase there, I don't think we can ever answer the question of death adequately until we understand it far better, because there are too many variables. And I don't think a case controlled trial looking at LABAs is going to answer that question either.

If someone is on LABAs, but lives a long way from the hospital, we're probably not going to capture that easily in a case controlled trial.

DR. SWENSON: Dr. Fleming?

DR. FLEMING: The answer to question A, as I see it, is that the assessment of this composite of hospitalizations, intubation, and asthma-related deaths is what I would call a necessary, but not sufficient scope. It is important to understand this.

The signal that we see, though, that is concerning us, certainly, the most is the issue about the more catastrophic events, the asthma-related deaths, the asthma-related intubations, and, as has already been stated, it's not at all clear that you

understand that simply by looking at another important component, but not as more frequently occurring hospitalization, but not as nearly as impactful to the patient.

So my sense about this is that it is important to understand this endpoint. It's also important to do the best we can to understand this critically important signal about asthma-related deaths and intubations.

It's been stated, is it possible to do this trial. To me, it all comes down -- everything is benefit-to-risk. There is considerable evidence of benefit to a broad segment of the population. There's also, however, a signal for a very significant and serious risk, uncommon, but nevertheless, of significant important relevance to patients.

Is there equipoise? I believe there surely is equipoise, and that is the classic setting where we can randomize patients into trials. So I wouldn't argue that this is a trial solely intended to address or rule out the safety risk. It's a trial designed to understand more effectively benefit-to-risk in a

setting where we really do have equipoise. To me, this is the critically important aspect to is the trial ethical and is it important.

Now, lots of other issues -- and I think I will defer these comments for a few minutes -- lots of other issues are going to come up in B and C as to whether it's feasible. I believe it is feasible, to address both of these issues. But I'll defer those comments until B and C.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: I think we should avoid talking about the details of the trial. That is, if we decide that the endpoint should be life-threatening events, in some sense, I think we should avoid, as a committee, discussing how to define life-threatening events, because I have great confidence in both industry and the FDA to work out these details over time. And if they decide to do a trial, they will work this out well. So I think we're not talking about -- we're wasting our time if we try to get into the details.

In terms of this first question, I feel that

the issue of hospitalizations has been adequately answered by clinical trials that have been already conducted. So I don't think that that should be a part of the primary endpoint of the proposed studies.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I'll try to avoid helping to design the details of the study. But I think that one of the questions that hasn't yet entirely been answered is what's the question that's being asked.

If the question is death and other life-threatening events, the design that's been proposed is probably not adequate to address that question. One way to try to address it is to use a series of surrogates that are reliable. I don't propose to be able to answer the question of whether noninvasive ventilation, ICU admission, et cetera, are reliable surrogates for death, but I think that needs to be explored.

Then the next question that I would ask is when that has been done and when those numbers are known, does that yield an N somewhere less than a million. If it does, then a randomized control trial

might be a very reasonable way to approach the question. If it doesn't, then it's difficult for me to imagine how an NRCT would address the question, and the FDA and the sponsors might be forced to go to some other sort of design.

I think the first question is what's the question and trying to address it through hospitalization, I agree with other speakers, probably doesn't address that question.

I'll just throw in one other comment about design. One of the things I noted from looking at the BADGER study is that that looked at the best step-up and one potentially ethically defensible approach to a trial would be to take people who need a step-up and step them up to a therapy that we think potentially has a safety signal, which would be LABA, or to step them up to another controller therapy, such as leukotriene inhibitors.

Again, I'm not an asthma clinician. I don't know whether those are equivalent. A trial has been done, I hear. That's it.

DR. SWENSON: Dr. Kramer?

DR. KRAMER: This is hard, because you have questions throughout and you have to insert them at times that may or may not be appropriate. But for a moment, I would like to make a comment that I also am concerned that we may be asking the wrong question by just completely fixating down to exactly what the non-inferiority margin is in a trial that would try to show the additional risk, if there is additional risk, of adding LABA to ICS compared to ICS alone.

I'm commenting on this from the perspective of having been in the December 2008 meeting and reflecting on what happened in that meeting. And since all of us weren't there, I'd like to bring us back to that for a moment, because at that meeting, there was no question -- there was a unanimous view that there was a rare, but serious and life-threatening side effect that was clearly associated with LABA when used without concomitant ICS.

There was uncertainty about the combination, which is why the FDA has posed the question they have posed to us. But it was a very interesting conversation, because even knowing that there was a

very rare life-threatening risk, the perspectives of the various people, even different groups within FDA and the committee itself, were quite varied in terms of what you should do about that.

There were some people that, because the -- as they went through and described the basis for approval in the first place, it was very clear that endpoints involving pulmonary function testing were the criterion that were the established basis for approval. And there were some people who had the view that, well, that's trivial when you consider it against life-threatening side effects and these drugs should be just removed from the market.

So in that context, I listened at that meeting and I listened today in the public hearing session to patients and prescribers and I heard something very different.

I vividly remember the 13-year-old boy and his mom who presented during that session and to that little boy, who spent a lot of his time in the hospital prior to being able to have a combination product available to him, and missed many school days,

he couldn't imagine that somebody would take that away from him. And we heard today the dissonance for clinicians who are treating these patients.

So I'd like to raise whether we're just trying to do the wrong study, because what I heard -- at that meeting, by the way, there was a statement that quality of life criteria by the overall score, if I remember correctly, the overall score was not clinically significant. It was better, but not clinically significant.

But what I heard patients and prescribers say is this is a real benefit and we need to measure these things that we understand, so we know what the balance is. As Tom Fleming has said, everything is relative, benefit and risk.

So I think that what we really should be talking about is addressing the public health question, the questions that patients and prescribers are facing when they have asthma that's uncontrolled. And we should be doing a study -- I personally think it should be a randomized controlled study -- to address the questions that these decision-makers have.

I can't possibly imagine anyone saying this is the exact amount of risk I have to exclude, if you don't put it in the context of what you trade off in terms of a meaningful benefit to patients and the prescribers can actually understand.

I'm not sure we've ever done a practical clinical trial, and defining practical clinical trial as one that is directed towards addressing the questions of these decision-makers, patients, and providers.

If you don't do that, then I do have some problems with the ethics. I mean, we joked about how hard it would be to say, "Look, I think this might kill you. Would you like to participate so I can see how likely it is to kill you?" That isn't very attractive. But I think that if you say to patients that you're trying to understand the balance, then it's much more acceptable, and that's exactly, I think, what the FDA is looking for.

Now, the question is, how do you do that. And I probably should do a disclaimer here, because I'm involved -- I'm really, with a very large

percentage of my time now, leading an FDA public/private partnership called the Clinical Trials Transformation Initiative. And if anything, this thing was started because we're realizing the numbers of questions we're having to address, as we've talked today and, hopefully, in a randomized setting, is increasing and our ability to actually conduct these trials in a practical way, at a reasonable duration, and a reasonable cost is going in the wrong direction.

Everything is going in the wrong direction. It's harder, it's longer, more expensive. And it's not just a problem for sponsors. It's a problem for society that we can't get these answers, and it's an abomination that clinicians can't, in our current system, actually enter their patients, as we heard here today, not because people didn't want to, but because we have a system that doesn't allow it.

So I'm going to get off my bias here. I, obviously, believe that we've got to find ways to do this more simply. So I'm talking long, but it's going to answer all the questions that have been posed, and I won't have to speak again.

So I think that we should do a large, practical clinical trial that's consistent with current treatment guidelines -- I think that's crucial that it's consistent with current treatment guidelines -- that would determine risk in the context of benefit that patients will understand.

I haven't heard anything about patients being consulted to ask them what the meaningful outcomes would be if they were trying to decide whether to use these products.

I got the impression from the 13-year-old boy and his mom that nocturnal awakening feeling like he was smothering to death was a crucial symptom, and I would think that would be an important endpoint. Days of school or work missed seems to be pretty objective.

Let me just say right here, it seems to me that, in today's day and age, with the electronics that we have, we should be designing ways to get this information in a prospective way during the trial with ways that would be fun for patients to submit.

Couldn't there be an iPhone application?

Couldn't there be an electronic device you would actually give to every patient and you'd get the information in real-time? I know people are creative. There's got to be ways that we can get this information as the trial is going on and we can get information about feasibility.

It would be a plus to participate if you had this fun device to submit your data on. And if you didn't submit your data, you're out of the trial, you get the device removed. I don't know. There's got to be some way.

The trial should be large enough to have the power to detect -- to be reasonably able to detect the serious endpoint we're talking about. Frankly, I disagree that we shouldn't discuss details of trial design, because I heard some creative suggestions around this table and I've been to a lot of these committees, and I think the committee members add a perspective that the sponsors may not have and the FDA is looking for. So I think the idea of ICU admissions, the idea of noninvasive equivalence of mechanical ventilation, I think we should look at.

Finally, I think the trial should enrich those populations for whom prescribers and patients need more information on benefit and risk, and, specifically, pediatric patients, adolescent patients, and African-American patients. And if you're doing it in the context of trying to understand how they benefit, then you can justify -- in actually enriching it, you could set limits of the number of adult patients that you would enroll in a trial.

Now, I'm going to go a little bit on to describe the description of a trial. So if you have patients that weren't adequately controlled on medium dose ICS that were randomized to LABA plus ICS versus ICS alone and it was blinded, this is outrageous, but I would love to see all three companies actually collaborate in one large international trial.

Now, you could say, well, these are different drugs. We heard the FDA say that. Yes. The FDA has inflicted class effects and class warnings and boxed warnings just because they're in the same class. So we're really getting an inconsistent view here.

If it's really important to understand the benefit and risk of this class of products, maybe we should do one trial around the world and maybe the companies that have products that are approved in pediatric populations could contribute more patients there.

Maybe we could leave it up to the doctors that are randomizing their patients. They would just randomize to LABA plus ICS versus ICS and the doctors choose which product, and you could have a max of one product. There are ways to do this, details to be worked out.

I do think that the agency should consider dropping the third principle in their February announcement, meaning specifically stating that LABAs should be withdrawn when the patient stabilizes. Number one, it conflicts with current treatment guidelines. I think that it does present an ethical dilemma for conducting a trial such as this, and I think the agency would be better served to actually gain the data first and then consider what to do after that.

Therefore, it's going to be necessary to get the trial done, I think, in relatively short order. I think five years is the max that it should take. I think there are creative ways to do that.

I think one of those that came out of the Clinical Trials Transformation Initiative we've been talking about is the idea of the reviewing division, the sponsor, the Office of Surveillance and Epidemiology, and the Division of Scientific Investigation, all together, up front, deciding what are the key parameters to monitor in these trials to assure the protection of human subjects and the reliability of the trial results, and only monitor those things; to consider central monitoring, for instance, in a novel way.

A large percent of the cost and time in trials has to do with things that may not add value to the ultimate endpoint, and, after all, these are approved products, this is a post-marketing trial, and it should be done in a real world setting and not inflict things that don't add value, but extend cost and time.

I also think that it would be important, if we're going to use these rare endpoints, to have central adjudication and I think very careful consideration to the regional considerations that have been raised by other members is important.

Thanks for listening.

DR. SWENSON: Okay. Dr. Kramer, you touched on a lot of points here. With the matter of time here, I think the one question of these three that hasn't been really discussed at any specific level is B, and perhaps we should take a few moments for comments around the answer to B.

I would just jump ahead here to people that actually have that. Could you just indicate to yourselves?

Okay. Then, Dr. D'Angio?

DR. D'ANGIO: I don't have a specific number, but I think that I'd echo what a lot of other people have said, that some of that number is going to depend on what the perceived benefits of these drugs are.

We've heard a lot of evidence that suggests

that people perceive that there's a benefit of the drug and it may be that a real, but small increase in the risk of catastrophic events is worth missing if the improvement in day-to-day life is good enough.

I don't propose to come up with the answer to that calculus, but I think that's the calculus that needs to be applied to this rather than one that's based on trying to reason backwards from sample size, rather than one that's achieved by trying to reason backwards from endpoints that may not all be in a single group, like hospitalization and death.

DR. SWENSON: Dr. Fleming?

DR. FLEMING: I absolutely agree with Carl that coming up with a margin, what it is we have to rule out. Again, everything is benefit-to-risk. So it has to be put in the context of given the benefit, as we understand it, what is the level of risk that we could accept or that would be acceptable.

So I agree with Judith that when this study is conducted, my belief is there are multiple -- I want to keep it as simple as we can, and yet adequately informative. So I believe that while it is

important to look at this composite endpoint, including hospitalization, it's also going to be important to look at the catastrophic events.

It's also going to be important, maybe in a well defined subset of sites, to be able to look more effectively at what is the benefit; so that when we're done, we can make this benefit-to-risk assessment. So missed school days, missed work days, asthma-related quality of life, nocturnal awakening, those kinds of measures would be extremely important, as well, in understanding this.

So I'll lay out my sense now, but, obviously, with the recognition that this is only an approximate sense, but it's the reason I think it is feasible to get the answer to all of these issues.

From the perspective of what I consider to be extremely important to gain insights about, which are the catastrophic events, what is that event rate? In SMART, it was 20 per 10,000. We saw in Salpeter, it's dropped to 3.2 per 10,000.

If we use the Salpeter estimate, one can rule out a fourfold increase. What is that? And by

the way, I'm going to make an assumption. I should lay out these assumptions up front. I'm assuming that this would be a six-month follow-up and, obviously, it could be three months, then we'd have twice the size; it could be 12 months, it would be half the size. But I'm going to assume it would be a six-month follow-up.

I also agree with some others that have argued that this would be flexible in that we would allow for a combining of the different products. It makes sense to me for those to be entered according to market share.

So my sense is pooling all of these results, particularly as it relates to the more major endpoints, such as the catastrophic endpoints, we'd be pooling across the products. For hospitalization, you may be able to answer a product-specific question.

But essentially, if it's six months of follow-up, with 45 to 50,000, a trial of 45 to 50,000, that would give us 80 percent power to rule out this fourfold increase, basically, translating to rule out a 10 per 1,000 increase in these catastrophic events over a six-month follow-up period.

To keep it short, that same size trial would allow us -- the FDA had talked about several designs for the hospitalization endpoint, ruling out a 20 percent relative increase, 30 percent relative increase, 50 percent relative increase.

Taking the more liberal side of that, a 40 to 50 percent relative increase, we could effectively address that issue, as well, with a study of 45 to 50000 people followed for six months; again, half that size if it's 12 months and twice that size if it's three months. Effectively, what that would give us is a trial with about 350 events in hospitalization.

The reason a trial of that size for hospitalization is important is that it's also going to be powered for key subgroups. And so if subgroups are product-specific assessments or assessments in the step-up or step-down context of the comparison or specific assessments for separate products, we will still have the ability to do what the AstraZeneca study design was talking about yesterday, which is having 88 events and being able to rule out a doubling.

So essentially, a trial roughly in the neighborhood of 45 to 50,000 people in adults that would follow people for six months would simultaneously be able to address, in a quite rigorous way, the effect on hospitalization and even to be able to do within key subgroups and in a collective way to be able to look at the catastrophic events.

One last thought. It could be argued that the true rate for these catastrophic events is even less than what the Salpeter calculation indicated. So my calculations are saying with 45 to 50,000, you're going to get 17 events, which is exactly what Salpeter had, and that is powering you to be able to rule out this fourfold increase.

If, in fact, we do this trial and we find out the actual event rate is far less than that, that, in fact, will be a very important insight, because we're working off a context where, in SMART, the Serevent rate was 37 in 13,000 people, which effectively is 26 events, 26 catastrophic events per 10,000 people. Salpeter says, no, it's now only 5.

Well, if we conduct this trial and it comes

back to the other comment, this is going to give us the ability to get absolute risk. If we find out we're not getting 17 events, that the rate is far less than that, this will be a very critically important insight that, in fact, it is true that this rate is far less.

So the bottom line is my sense is that we can do this trial in a way that allows us to merge results across the products and get product-specific and even subgroup-specific insights about effects on hospitalization, and, also, though, aggregate the data to get very important additional insights about the catastrophic events; and, also, in subgroups of patients, to be able to enhance our understanding about what the efficacy is to allow us to make this more informed benefit-to-risk judgment when we're done.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: It is shocking to me that Dr. Mosholder and, probably inherently, Dr. Fleming, regard the data in Salpeter as showing an effect of this kind. There is no statistically significant

evidence that the combination increases mortality.

The data you're quoting and that Salpeter confuses in her paper very badly is suggesting that there's a death signal. The death signal entirely comes from salmeterol or from LABA used on its own. You will not get an answer out of a control trial of that kind.

I would like to echo what Dr. Redlich says, that control trials have enormous problems. They're very selective in the patients that are enrolled, and that's been true for every condition that's been put.

But let me put a very specific issue, which is an issue of designing the control trial, and a question to AstraZeneca and GSK. Do inhaled steroids successfully protect against the harmful effects of LABA in smokers?

The reason for asking the question is because there are several studies that show that inhaled steroids are relatively ineffective in smokers, and, for this reason, smokers are excluded from most of the studies.

In my emergency room, 50 percent of the

adults who are smokers, with asthma, coming in with asthma, are current smokers. And smoking in the USA today is very strongly associated with poverty, and that's where we see the mortality signal. And I suggest that 90 percent of the designs that are being proposed here will not address that issue at all and that that's the issue we actually need to know.

But first, I'd like the two companies to address the issue, do they have any data to answer whether inhaled steroids protect against the harmful effects of a LABA in smokers.

DR. SWENSON: I'll ask the two then to make very brief comments here.

DR. KNOBIL: Kate Knobil, GSK. We don't have any analyses of these more severe asthma-related events, including death and hospitalization. And I would say we'll have to separate whether the effects of LABAs are harmful or whether it was an effect of poorly treated asthma without an inhaled corticosteroid.

We do have the GOAL study, which was done in Europe, in which about 20 percent of the people

enrolled in that study were smokers, as studies in Europe are generally different in that respect.

What we found was that, in general, in patients who smoked, they had a lower response in FEV-1 both to inhaled corticosteroids and the combination, inhaled corticosteroid and LABA, but the relative effects of both were about the same.

However, when we looked at exacerbations requiring oral corticosteroids, there was still that same reduction in exacerbations from baseline with both inhaled corticosteroids and the ICS/LABA, Seretide. But there was a significant reduction with those receiving ICS/LABA versus receiving the ICS alone.

So while, for FEV-1, there seems to be a general decrease in response, overall, the exacerbation rate seemed to be equally positively affected, even in smokers.

DR. ANDERSSON: Generally, in the asthma studies from AstraZeneca, smokers --

DR. SWENSON: This is Dr. Andersson.

DR. ANDERSSON: I'm sorry. Dr. Tomas

Andersson, AstraZeneca. We normally allow smokers up to 10 pack years. The reason for not allowing more than that is that we want to exclude COPD patients.

There is an analysis that has been published rather recently from the large SMART study looking at budesonide versus placebo on the smokers and I believe that it showed that there is a beneficial effect of budesonide compared to placebo, but probably that they have a higher event rate.

When we look at predictors for exacerbations in our studies, smoking does not fall out as a major factor, but, of course, it's only a fraction of the patients that are smokers.

DR. FLEMING: Dr. Swenson, could I just briefly clarify what may have been a misinterpretation in my statement? Just very briefly.

DR. SWENSON: If you'll be brief.

DR. FLEMING: Very brief. The reference that I made to the Salpeter paper was simply to say if one is ruling out a fourfold increase, 80 percent power, you need 17 events, is it feasible you could get that. So I was just using those data not to say

they indicate an excess risk, but to calibrate what the risk is.

So my simple comment was if you use SMART, you would say that risk is 26 events per 10,000 people followed six years. If you use Salpeter, you would say it's 5. I'm not saying anything about whether that's causal. I'm just saying what's the baseline rate, and my calculations use an assumption of 3.

So I just wanted to put context around the sample size calculations, not to say in any way Salpeter is reliable or unreliable evidence.

DR. SWENSON: Okay. At this point, we should move on to the pediatric discussion here. That's going to be the second question here. And I will ask that those with pediatric knowledge be the ones to speak a bit more forcefully here.

DR. JENKINS: Dr. Swenson, could I just ask -- before you move on to pediatrics, could I hear some feedback from other members of the committee? Dr. Fleming, on several occasions yesterday and today, has argued for maybe a fourfold excess risk that you would be looking for for the catastrophic events.

So can I hear some feedback from others around the table? Is that in the ballpark of what you would find acceptable in this type of a study?

DR. SWENSON: Dr. Ownby?

DR. OWNBY: Having had a number of these discussions with patients and parents, it seems like when we talk about a small increase, these 20 or 30 percent increases, no one gets very excited.

Somewhere between two and fourfold or, more likely between four and tenfold is where I think patients and parents really begin to show very substantial concern. So I think something in the fourfold or greater range would be far more informative to clinicians and much more likely to change behavior, given all the other things that have already been discussed.

DR. SWENSON: Dr. Redlich?

DR. REDLICH: I've never taken a penny from a drug company. But it seems that we already have a rather extensive literature that the risk of this combination therapy is extremely low or maybe nonexistent, as in combination, but it's very low, so

low that we can't design a study that will detect the magnitude of the effect.

So it seems like there are a lot of important questions as far as asthma treatment; how you should step down, whether subgroups, such as smokers -- tailoring treatments to those groups.

But it doesn't seem that mortality from combination therapy is really the -- I would say that that's probably an unanswerable question, better than what we've already answered. Life has some uncertainty. So we know the risk is very small and I doubt that any other study we could possibly design would come up with a better answer.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: I don't think we know that. At the last advisory committee meeting, I estimated the risk, based from the study that was presented, 1 in 700 and since I usually don't believe in subset analyses, that's what I considered the risk to be.

I think that when this paper comes out and is debated in the literature, there will be a substantial number of people who will believe that the

risk is 1 out of about 1,400, and that is a reasonable estimate of the risk.

So I think that to say that the risk is minimal -- first, I really want to focus on absolute risk. I think relative risk is useless here. You know what I mean? I think I wouldn't talk about relative risk ever. But the absolute risk is what's important when you have a real benefit, and I think we know there's a real benefit.

So I think we're really talking about absolute risk and I think that what will happen after the Salpeter article is debated is that there will be plenty of people prescribing these drugs in face of a risk of 1 in 1,500 that they may think is a possibility.

They may not think of that as their estimate of the risk, but it's going to be what they think is a possibility, and I think that we need to rule out that risk. And I think that the study that Tom has suggested would rule out that risk.

In fact, one part of me says why not let the companies do what they plan to do, because, in fact,

when you add up the number of sample size that each company projected for their clinical trial, it adds up to roughly the same number of patient years.

So really, what we're really talking about is a planned meta-analysis or a designed meta-analysis, which I don't know if this is the first design meta-analysis ever done or not. Tom would probably know, because he keeps track of these things better than I do.

DR. REDLICH: I'm sorry. There are several other meta-analyses that have been done, some of which were in our material. So I'm not sure why we're putting so much weight on --

DR. SCHOENFELD: Well, I just think that some people will put weight on it, at least Dr. Salpeter did, and I think that it's out there and it's believed by some people and I think that it's what we'd like to rule it out. And if we can rule it out, we would like to rule it out so that we may know that the risk -- if it turns out that in this trial, let's say, or this planned meta-analysis of the three trials that have been proposed -- it turns out that after the

first 3,000 or 4,000 or 5,000 patients, there's no events in either arm or no events in the Advair, in the combination arm, we can decide to stop the trial, because we'd say, "Okay, the risk really is 1 in 10,000 or 3 in 10,000 and not 1 in 1,500 and given the benefit of these drugs, we don't have to go on."

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: But Weatherall and Richard Beasley is a much more respectable study. Those are people who have been in the field who know something about it. Salpeter is not in the field, doesn't know anything about it, and, as far as we can see, her analysis is extremely biased.

Remember, she starts with over 200 studies, rejects 80 of them out of hand for no reason, then rejects another 70 for other reasons that we're not clear about, and ends up analyzing 10.

That is the whole issue about meta-analysis and meta-analysis is very faulty. I don't buy the conclusions at all and there isn't a signal for death in true combination therapy. There is no significant data.

DR. SWENSON: Dr. Fink?

DR. FINK: Just a comment I would like to make. I am concerned about the idea of combining data from the different studies. That's based on the assumption that all the inhaled steroids are equivalent, and we do not have any data to support the statement that these inhaled steroids are equivalent. They have never been studied for hospitalization or death endpoints.

So I think that you can't really separate out the effect of the LABA if you don't know that the inhaled steroid that they're combined with or compared to are equivalent, and I would be very careful about combining data from fluticasone and budesonide and potentially some other steroid into one analysis.

DR. SWENSON: Dr. Ownby?

DR. OWNBY: At the risk of being labeled a heretic here, and, I'm sorry, I don't have the PDF to pull up, but there was a 1997 study in the New England Journal entitled "Discrepancies Between Meta-Analyses and the Subsequent Large Randomized Clinical Trials," and my memory of that study is that half of the large

randomized trials shows that the meta-analyses were totally off base. So I feel that we're putting a lot of weight on meta-analyses when that's probably not the best way to go.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: In an attempt to answer the FDA's question, I think that the way I would view an acceptable number for the outcome would be that it's a clinical question; that it's based, as Dr. Schoenfeld said, on absolute risk or on risk difference between -- and there may be no risk difference between the two arms.

But I think that the question is trying to establish what the absolute risk is, whether there is a risk difference, rather than deciding on some number for relative risk, and the relative risk is really back-calculated from what we think the risk is.

I think that that's probably the more relevant question for clinicians in trying to balance risks and benefits, in this particular instance, where the events are relatively rare. And missing an apparent 1.25-fold or 1.5-fold or even 2-fold risk

might be acceptable if the benefit is high enough and might be acceptable if the baseline risk is actually very low.

DR. SWENSON: I'd like to add a point that this might be somewhat unprecedented, but we have had the discussion around the practicing physicians and the patients not having a full say in this, as to whether the FDA would consider in some way a polling in a way that it would be done to assess how practitioners and patients value quality of life, which is clearly improved with the combination, as opposed to bounds of this theoretical adverse risk of death and severe adverse events.

Perhaps with that knowledge, they then could begin to better define and calibrate what kind of statistical limits on threefold, fourfold ranges on some of these signals. This would bring in, I think, the important point that, for many people, these drugs really do improve life and we possibly ignore that in just focusing in on these adverse events.

Well, at this stage, then, let's move to the pediatric question here and have thoughts as to how a

pediatric study would be defined and bounded.

DR. FLEMING: Is there time for one brief comment on this question, one before we leave it?

DR. SWENSON: All right, one more.

DR. FLEMING: Okay, very quick. The Salpeter meta-analysis, to my way of thinking, is a clue. It's the reason -- it's not a reliable answer, I believe. It's the reason, I believe, we need more research.

I believe we don't have an adequate answer at this point for the LABA plus ICS against ICS, although I will say it wasn't just a dozen studies. It was selectively looking at randomized trials where there was at least three months of treatment, by design.

It was selective in that way, but it included, beyond those dozen studies, many other studies that contributed no events. So those other studies are relevant to understanding absolute increase, but they don't contribute to the estimate of relative risk.

So the ones that show up in the table

contribute to the relative risk. So I just wanted to clarify. My understanding is that meta-analysis is much more comprehensive than a dozen studies.

Relative to the combination, I also concur that it would be ideal to understand definitively the effects of each individual type of regimen as opposed to the class, but basically saying what's LABA plus ICS against ICS.

I think the design that we talked about or a version of the design that we talked about for question number 1 does allow some considerable insight for the more common endpoints, like hospitalization, by specific agent. But it's not going to be feasible to answer it by specific agent for the catastrophic endpoints.

So that's where it compromises. It says for the catastrophic endpoints, we're going to look at the broader question of LABA plus ICS against ICS.

DR. SWENSON: A question to the statisticians.

DR. BRITTAIN: We've heard Dr. Fleming suggest we need a trial of 45 to 50,000, which we

know, even with collaboration, will be challenging. So my question is, you all have been busy with your calculators, I just wonder -- first of all, I had a sense that patients don't make their distinction on whether it's 1 in 1,000 or 2 in 1,000. I don't think that's how they think about these.

So have you done a calculation to say what kind of ability would you have to define this, likely, risk difference if you studied 25,000 patients, half as many patients?

I know that's bad to start with the size that might be reasonable and doable, but we also have agreed that if it takes too long, it'll be irrelevant and we'll never get an answer.

So I'd just like to know if there's something in between.

DR. SWENSON: Dr. Fleming?

DR. FLEMING: That's a great point and it's my sense that this proposal is trying to hit that in between. This could readily be -- could, importantly, be a lot larger to give us a lot more insight. But I definitely concur with a lot of folks who have

indicated that timeliness of this answer also matters, and, hence, feasibility does play into this.

So in response to Dr. Fink's excellent point about where you can pool and where you can't pool, it's precisely to allow for the compromise to what's feasible and timely to say we're not going to get the catastrophic answer specifically by agent, although we can, in a timely, feasible way, get insights about the hospitalization issue globally in a rigorous way, as well as by specific sub-products.

If we had half that, would we get useful insight? Yes, we would, but now the power is substantially less; i.e., the ability to rule out an excess risk is going to be substantially curtailed if we had half this amount of information.

DR. SWENSON: Any other of our epidemiologists wish to comment? Dr. Brittain?

DR. BRITTAIN: Yes. I guess I would just like to make a plug for the 12-month study. It seems like it's a good idea, in general, to have the full year, because of the seasonality of asthma, and that halves the study.

DR. SWENSON: Dr. Fink?

DR. FINK: Just a comparative comment. We're focusing on mortality here and it seems like we're almost assuming that asthma is a disease that doesn't affect quality of life and quality of life isn't important in asthma.

If you take a disease such as rheumatoid arthritis, where the native disease rarely would cause a hospitalization and almost never a death, we have accepted the use of drugs that cause significant hospitalizations and deaths to improve quality of life.

I don't see why asthma is any different and, clearly, we have a class of drugs here that improve quality of life and accepting some risk, probably less than what is accepted in rheumatoid arthritis, is very justifiable to improve quality of life.

DR. SWENSON: Dr. Ownby?

DR. OWNBY: I think one of the points that we've touched on, but I find somewhat lacking in our discussion right now, is I think we need to accept a broader definition of severe adverse events and a

higher level of risk in these studies, because I'm particularly concerned about a number of subsets.

We've mentioned African-Americans. We've mentioned Hispanics and the multiple groups that are rolled into that. We haven't mentioned the broad census category of Asian-Pacific Islanders, where there's a huge degree of heterogeneity in their asthma risk.

But I think all those are very important, because as Dr. Camargo mentioned, the overall risk of asthma is declining; but if we look at the relative risk of death for African-American youth, that is, between 10 and 20, versus Caucasians, that has steadily gone up from about a 6-to-1 to a 9-fold increase in death.

So I think whatever study we need, it should address some of these subpopulations with adequate power. And, unfortunately, I know from experience of working in public schools in Detroit that even with substantial incentives and, essentially, what I thought was a zero risk study, that is, looking at a computer screen for 30 minutes four times, recruiting

those youth was very, very difficult. We never achieved more than 25 percent. And that raises all the issues of bias in your sample. So I think that we need to keep those facts in mind.

DR. SWENSON: I think we do need to move on. I'm going to move to the pediatric issues, and we'll take any questions toward the questions raised about the pediatric study.

Dr. Joad?

DR. JOAD: This is Jesse Joad. I'm a pediatric pulmonologist. So just to address those questions, I'm thrilled that we're going to do a study in children and I can see that hospitalizations have to be the endpoint and not death for this group, just because there are so few.

Ninety-five percent is fine and alternate endpoints, I don't think there can be any, because there are so few. It would have to be BiPAP, intubations and death, and I don't think we can do that.

The caveat I would like to mention is I think the study should be done according to the

guidelines and not according to what's been approved by the FDA, or it won't be at all real world; that it does have to allow -- that's coming up in another question -- but for people to up and down the inhaled corticosteroid dose, so that it would represent real world use.

I think Novartis should do a pediatric study in the pediatric age range, because they do have an approved drug for children. And the African-American issue is really essential. I think I remember right that when Advair was approved -- and, please, if I'm wrong, let me know, but I think it was 98 percent Caucasian. It was just amazingly non-diverse, even though it was supposed to be diverse.

I think there just has to be some teeth into the recruitment of African-Americans, and one group that's working on it is our CPSC, through the NIH. They have a community engagement corps for all of them and perhaps the companies could be working with that group on bringing African-Americans in as study subjects.

There's a lot of good reasons why African-

Americans don't choose to be in studies and we have a lot of work to do, and this is a big opportunity to really make an effort and do the work that needs to be done to get that part done.

Thank you.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: I'm not a pediatric pulmonologist, but I would be interested in the pediatricians' opinions on the endpoints for the pediatric study. Again, asthma-related hospitalizations implies a severity of illness, but I would wonder, in kids, whether the pediatricians would also be looking at something or it would be worth looking at something like absenteeism, inability to participate in exercise, the grades, that kind of thing that is important with children, a little bit different than adults.

DR. SWENSON: Can we have some pediatricians' opinion on that? Dr. Fink?

DR. FINK: I agree. I think one of the issues is that many drugs are used off label, and we have pediatric patients, particularly adolescent

patients, who may be on a long-acting beta agent not because of the severity of the asthma, but because they want to play in sports at a competitive level and it's the only way to control their asthma symptoms during sports. Otherwise, they would be low dose inhaled steroid alone.

Those patients are at extraordinarily low risk, probably, of any death, probably even low risk of hospitalization. So I don't know that we can address that group, but I would like to reinforce what Dr. Joad said.

Real word studies I pediatrics, I think, hospitalization, with a collection of sort of the severe events secondarily is important, but we do need to look at multiple products. Even if we only look at a single product, entry criteria have to allow patients who have been on any LABA to go into the study.

There is significant use of Advair at other doses than 100/50 in pediatrics, as well as significant use of Symbicort. I think probably significantly less use of foradil under age 11, but at

least Symbicort and Advair at other strengths are commonly used.

DR. SWENSON: Mr. Mullins?

MR. MULLINS: I wanted to comment on the issue of recruitment of subpopulations. And I think that --

DR. SWENSON: Mr. Mullins, are you focusing on the pediatric group?

MR. MULLINS: Yes, in pediatrics, that particular group. And I think it's important to understand that oftentimes, the treatment and the therapies given to young people, adolescents and pediatrics, that whole audience, the decision-making for managing their health care is being done by second and third parties.

So I think that we need to take that into account. I think that there are certain influences on the young person that your interpretation of an adverse event might be different than their interpretation of an adverse event, because the filters that they use for adverse event are different than yours.

So I think that we need to broaden -- I like what Dr. Fink said about broadening the secondary endpoints to include things like emergency room visits. I like that. I think partnerships -- the reason we have challenges with subpopulations is because of trust issues, when clinical trials wouldn't speak to that.

I think when you come into a community and you mix in the word "death" with a large corporation, they don't know you. So that's a very prohibitive combination of different terms. I think through partnerships, peer-to-peer suggestions and counseling, partnerships with churches, with school nurses, I think you will get the participation levels that you need.

I think that we do need to broaden our endpoints to include other decision-making aspects of the subpopulations that are quite different than what we're looking at now. So I did want to comment on that.

I think things like looking at data from school nurses, days of work missed by the parent,

because the economic issue is very important. If a parent misses a day of work, that's a major event in certain populations.

So I think we need to think about this outside of the sanitized microcosm that we have in mind about how we feel health care is managed by all populations, because health care is not managed the same way by all populations.

Thank you.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: Just a couple of brief comments regarding the question on the slide. First is that I would go back to the comment that I made earlier and that others have also touched on about the definition of asthma-related and the requirement for a critical look at how that's defined.

The other question that I have is, I understand that in kids, that death is an even more rare outcome than it is in the adults and that for reasons related to the rarity of the event, that it's not good as a sole endpoint. But I guess I don't understand why we wouldn't include it -- why we

wouldn't use the same kind of composite endpoints that we would consider for adults.

I think the death of a person at any age is a tragedy. When it happens to a child, a preventable death is just horrible. And so I wouldn't want that information to be lost as we go forward.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: A couple of different comments. One is to try to address some of what Mr. Mullins said. I think that one effective way that investigators at our institution have been able to get buy-in from the community in our city, particularly of people who are of lower socioeconomic status, is to go into the schools, and that's potentially a very viable way of trying to partner with an institution that sometimes is a little bit more trusted than the medical institutions are. So I'd second the idea of partnering with people like school nurses to try to enroll people in populations who might otherwise be underrepresented.

Then to try to address question A there, I think that we face the same thing that we did with the

adults, except that it's magnified death is even rarer in children. We do need to try to understand what the benefits are.

Many of the things we're talking about are potential benefits of adding a LABA to ICS and we need to understand what those benefits are. That's been looked at many times. But particularly if we're able to look at those benefits in subpopulations that haven't been well studied before, that's important. But we need to keep our eye on one of the reasons that we're here, which is trying to figure out whether there are potential harms.

This may be a situation where some of the observational methods that have been talked about are going to be the only way to address these very rare events.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: I'd like to ask the pediatricians and the people who treat adults why we need to treat, in this particular instance of estimating risk and risk of mortality and catastrophic events, why we need to separate children and adults

and why we can't simply pool these data.

I think that this has been the biggest problem. Pediatric trials are a big, big problem, because often it's very hard to do an adequate trial in children. And I think that in many situations, we extrapolate from adults to children and I would think that without the data, we would do the same here.

So I'd like to ask people for comment on that, because if I didn't have extra data, I think that's what would happen; we would extrapolate.

DR. SWENSON: Okay. We'll close it out with responses to that question from our pediatricians. Dr. Fink?

DR. FINK: Yes. You could look at it that way, but everyone has always said, pediatricians, kids are not little adults. Look at the difference in drug approval. Right now, in pediatrics, the only approved drug we have is Advair 150.

My answer is we shouldn't be doing this toxicity trials. We should be requiring NDAs for a variety of other agents in pediatrics. There is a need for a good pediatric trial looking at LABAs as

add-on therapy.

In pediatrics, asthma, ER visits and hospitalizations, number one or number two admitting diagnosis at essentially every pediatric institution I the country and make up between 20 and 30 percent of all pediatric hospitalizations.

The health care burden in pediatrics of asthma admissions is huge, and that needs to be addressed. And we need to know, do LABAs add to that or, hopefully, subtract from it.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: Regarding Dr. Schoenfeld's reference to extrapolation and pooling of information, I actually think that that's an important point to kind of kick around a little bit. If this isn't the exact forum for it, I hope it happens in another forum.

But I think the idea of extrapolation is one where if we had a very clear safety signal in adults, then we wouldn't be asking the question in kids. We likely wouldn't be asking the question in kids. And this gets at some of the ethical questions that were

referred to yesterday.

I think that a pediatric safety study has to presume that either there's inadequate safety data in adults or that a drug has been shown to be safe in adults. That's my opinion on this topic.

I know that Dr. Nelson has been here, I'm not sure if he's still in the room, but he may have some insights to share regarding that, as well.

DR. SWENSON: Dr. Joad, you had a comment?

DR. JOAD: I'll wait for Dr. Nelson to speak.

DR. SWENSON: Okay.

DR. NELSON: Let me just briefly address the extrapolation issue. Extrapolation is used for efficacy. The definition of extrapolation, which is actually in the FDA amendments, is that the course of the disease and the response to treatment are similar enough to be able to extrapolate efficacy.

I won't comment necessarily on the limits of that. That's a decision that the division makes in consultation throughout the FDA, but that's the standard approach.

Extrapolating safety and dosing, I think, is a dangerous thing to do. And if you look, actually, at the pediatric studies that have been done under either exclusivity, BPCA, or under PREA, the required studies, you end up often with roughly a third that may not show efficacy, roughly a third that will show new safety signals, and roughly a third that would say that the dosing was wrong.

So I would just say, as a general rule, you need data to support that decision. You don't extrapolate in the absence of data.

DR. SWENSON: At this stage, we're behind schedule and we should take our lunch break. I'd like to keep it to 45 minutes so that we can resume at 1:00. Thanks very much.

[Whereupon, at 12:15 p.m., a lunch recess was taken.]

A F T E R N O O N S E S S I O N

DR. SWENSON: Welcome back. We have still a considerable amount of discussion to get through here in a limited amount of time. So I'd like to proceed as judiciously as possible.

The FDA has asked us to at least look at again at point 2B, because our discussion hasn't touched on that enough. And so let me open it up to anybody who has an opinion about the acceptable level of risk for LABAs in this LABA plus ICS versus ICS trial and 95 percent confidence intervals on that risk.

We heard Dr. Joad give the affirmative on that. Do we have any other thoughts? Dr. Cnaan?

DR. CNAAN: I would like to respond to this question to Dr. Schoenfeld, basically, who asked why do we need to study separately in pediatrics to begin with, which then speaks also to 2B.

As noted by somebody else before me here, that children are not little adults. Where it translates here is that we've been hearing that their management and the prescribing is different in the

children than in the adults; where, also, we have a dosing issue.

Most of the pediatric studies, or many of them, are dosed based on size. We're talking about a range 4 to 11. Here, we have devices that don't allow us to do it. We have very few choices. So it would mean you have a dose range in a way that we don't usually do in kids and we're going to be forced to do here, which might give a different safety signal.

We also have the graph that we saw yesterday that showed the increased hospitalization rate in the younger kids as compared to the 12 and older. So it may or may not be a different issue. But for all of those reasons, to get the pediatric signal swallowed in an adult study, I think, would not be good. And I think if we need to study, we need to study the pediatric question separately.

One additional comment I have is to Dr. Rosenthal's comment about including the death as a composite. We have to do it the way Dr. Rosenthal suggested, because imagine if you had a death that was not after a hospitalization, that was outside; then

you would end up in an ICP study, including deaths where they're not hospitalized. That would be pretty wrong.

DR. SWENSON: Okay. So you've made some important points, but do you have any feeling about this specific question and the confidence intervals, assuming that a pediatric trial is done?

DR. CNAAN: I think we need to base it on the numbers that were presented yesterday for the 4-to-11 age group.

DR. SWENSON: Dr. Fleming?

DR. FLEMING: Let me try to basically answer B, but since I haven't commented on 2, I'd like to follow-up and agree with the comments that have just been made.

Basically, I agree with most of the comments that have been on question number 2; that, in essence, the endpoint that we will focus on would be the more inclusive endpoint than asthma-related hospitalizations.

I definitely agree it's asthma-related death, intubation, hospitalization, if any of those

occur, they would count, but acknowledge that, in essence, that would be a hospitalization endpoint.

My own sense about B is an approximate sense, but being enlightened by the very, very informative FDA analysis by Drs. Neustifter and Levenson, their overall analysis indicated, in a pediatric population, we might be looking at a background rate that could be 1.4 percent to 3.2 percent per year.

Thinking through this, as Dr. Schoenfeld has, as to what's the absolute risk, obviously, that's something that depends on nature of benefit. My own sense about this is in an endpoint that I would actually hope would be benefitted and might be benefitted, it would surely be problematic, I would think, if we had an increase of 1 per 100 person years in hospitalization or in excess of 1 per 100 or 2 per 100, which would translate, in a relative risk sense, to ruling out a 67 percent relative increase of 1.67.

So if we were using that as a guide, it would take a trial with about 160 events. Those 160 events would take -- if we were following people for

six months, for example, it would take 10 to 23,000. So the size of the trial would be 10 to 23,000, if we were following each of these pediatric patients for six months.

I would, again, concur with the idea that this could be done in an aggregation across products. So this wouldn't be a separate trial for each sponsor, but what we would get in the aggregate evidence.

I also think that we wouldn't need to use all of these patients for assessing efficacy, but at selected sites, it would be very additively informative to understand as clearly as possible what the efficacy is, again, in tangible measures, days of school missed, asthma-related quality of life, nocturnal awakening, et cetera, so that we can better put into context what this risk is against the benefit.

Unfortunately, I acknowledge we're not going to get definitive evidence about asthma-related intubations and deaths in the pediatric setting. Even if we used the overall Salpeter estimate of .064 percent, we'd only expect six events, and it would be

lower in pediatrics. So we'll probably have zero or one event, so it will be a very small number.

In essence, on that measure, what I would expect we'd be doing is, in essence, doing an aggregation of that experience with the adults to get a global sense of what the LABA plus ICS against ICS influences on those measures -- what the influence is on this catastrophic endpoint; obviously, though, if not entirely, mostly driven by what we see in the adult setting.

So essentially, the answer to question B, it seems to me we should be ruling out something on the order of 1 to 2 excess events per 100 person years, relative risk 1.67, probably a 10 to 23,000 person study at the six months follow-up.

DR. SWENSON: Any other thoughts to that? Dr. D'Angio?

DR. D'ANGIO: Again, similar to the adults, I think that some of this is a clinical question, balancing the benefits that people see against what kind of risk would we not want to miss in these drugs.

I agree with Dr. Fleming that probably an

absolute risk difference of 1 to 2 percent is probably a reasonable thing not to want to miss, which is what a non-inferiority trial is all about.

DR. SWENSON: Dr. Fink?

DR. FINK: I guess a critical question for design of a pediatric trial, though, is would FDA grant a waiver to use non-label drugs in a pediatric trial without pulling an IND and providing safety data and dosing studies prior to use of the IND, because if not, the only drug we really have is Advair 150, with potentially add-on fluticasone.

We could not use Symbicort. You could use foradil, but we've said we want a combination product in pediatrics. So it would limit us to a single moiety for the study.

DR. SWENSON: Okay. Dr. Joad, did you have a comment?

DR. JOAD: I just wanted to sort of second what Dr. D'Angio said about maybe this is the place to consider a case control trial, because we do -- I'm worried that hospitalization sits in the good side of what LABAs do. It decreases exacerbations, improves

symptoms, does all these things, and at least the GSK data shows decreased hospitalization.

So if what we really care about in kids is death, maybe this is the place in children to do the case control study, and I don't totally understand the downside of that. But we're not going to get it with this. So if it's possible that it will help, I think it should be explored.

DR. SWENSON: Okay. Well, let's keep that in the back of our minds, because I think it'll come up just a bit later. But there being no other comments to this, let's move then to question number 3.

The question posed here is that given this hypothesis, we need to discuss the disadvantages and advantages of study design in a real world approach where patients are enrolled and allowed titration of their inhaled corticosteroid compared to a study design where it remains fixed, and which of these designs would be more appropriate to address the safety concerns of LABA in the treatment of asthma.

We'll start with some comment about adults

and adolescents and then move to our favorite group, the kids. Okay. Dr. Kramer?

DR. KRAMER: I just think it's critical that we do the relevant study as patients would be treated in practice, and I can't imagine that anyone would just keep people on the same dose if they're continuing to have symptoms.

I think you need to allow this in both arms, and I think the need for additional ICS would be an endpoint in terms of a lack of efficacy, at the least.

DR. SWENSON: Dr. Roberts?

DR. ROBERTS: I'd just like to take the opportunity to say that while I understand the theoretical arguments for randomized control trials and against the nested case control study, I continue to be haunted by the issues of the feasibility of enrolling and worry that they would drag on and interest would be lost and meaningful results would not be achieved in a timely fashion.

I think an observational study would be an excellent opportunity to better characterize asthma deaths with regard to all prescriptions, frequency of

access to care, co-morbidity, and perhaps, in a design different from what is presented by Dr. Camargo, other exposures that may be predictors of asthma deaths besides treatment.

But back to the question. I believe that a real world study is probably the only way to go, as long as it adheres to treatment guidelines. And I would ask that if you have a patient poorly controlled on increasingly high levels steroids, would you allow them to stay in the study if switched over to the LABAs?

DR. SWENSON: Dr. Cnaan? Okay. Then, Dr. Rosenthal?

DR. ROSENTHAL: Just real quick, I'd just like clarification for why we're considering adolescents in the adult group instead of in the pediatric group.

DR. JENKINS: Well, that's more of a historical -- generally, adult studies have enrolled down to 12 years of age. So that's just a historic factor that predated a lot of the pediatric legislation.

So if you want to move adolescents down to the pediatric group, that's fine, as well. It's just many of these studies, including the SMART study, enrolled patients down to 12.

DR. SWENSON: Dr. Krishnan?

DR. KRISHNAN: Sure. I would like to second some of the comments made here. If we're after real word exposure and real world events, then we need to measure excess risk in the real world; and, excess risk in the real world does not at all approximate what you would find from a randomized clinical trial, because physicians and patients don't behave the same way as during trial conditions.

One example of this concept is that there have been a number of people both on this committee and elsewhere that have published studies about low adherence to medications, and that also will mitigate risk and it'll affect risk.

So that's one example of where patient behavior and potentially differences in prescribing patterns by physicians will differ from what you're going to conduct a study to answer.

So if the intent is to understand real world risk, I, once again, will recommend that we think about observational study designs and, again, this is where a nested case control study comes in.

I'd also take this opportunity perhaps to address a point that Dr. Schoenfeld had made earlier about whether it's possible to calculate the actual event rate in a case control study.

I had the opportunity to talk with him privately and I wanted to make this, as well, as part of the public record, which is one of the advantages of a nested case control study is that the case control study is done within the context of a cohort and as long as you're able to define that cohort, you will be able to calculate the event rate, the natural event rate of whatever it is you're looking for.

So these are very detailed issues that will need to be discussed, I think, in another forum where we understand better what other different observational study designs that are possible, what are the limitations of the datasets available, and so forth. But a nested case control study does allow

you to calculate baseline risk.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: Obviously, the real world issue is, obviously, what we really care about. We're dealing with a situation where, as a result of changes in treatment and perhaps the guidelines and introduction of combination therapy, the mortality rate for asthma has been declining steadily and is maybe at historical lows in the Caucasian affluent community; and, therefore, designing studies that actually address the real world population that is at risk.

If we don't do that, I think we'll be faced -- we could do a large study on traditional control trial basis and enroll large numbers of affluent children, insured children or insured young adults, and, at the end, no nothing about the reasons for the continued high rates of mortality among African-Americans living in poverty.

In addition, the case control approach definitely answers some answers to that. I think it'll still be extremely challenging to work out why

the mortality is occurring, but we can certainly address the issues related to LABA and combination drugs, and I think that that is a reasonable approach.

I think this control trial of 24,000, where it will not be in the populations that we're really concerned about, because very few control trials -- certainly, the idea of enrolling 24,000 children and getting that into the inner city is completely unlikely. That's not going to happen, and it's certainly not going to happen, and I think that's another issue that we need to put into the equation here.

If the new labeling instructions are put out and suggest that everyone should drop off Advair straightaway or drop off combination drugs straightaway after three months, it's going to be extremely difficult to do anything with this.

Furthermore, the new labeling guidelines are going to add more fear to a disease where fear is one of the key things that we spend our time treating patients to try and stop, get them away from it and get them active.

Fear is a disaster, because that's what lead people to stop doing physical activity, I'm afraid of my wheezing, and then they get overweight, they get deconditioned, and their whole condition gets worse. We spend most of our time in clinic not encouraging fear and discouraging fear, encouraging people to live normal lives.

If labeling is put on that says the normal drug used for these things is going to kill you, that is extremely unhelpful in the management of this disease.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I wanted to second Dr. Roberts' comments about the potential feasibility of thinking about a case control study in this situation. Again, the only way to assume that it's reasonable to go through with a randomized controlled trial is if there is a composite outcome that is a reasonable surrogate for death or other catastrophe, and so far, I haven't heard one in the study designs that is that. So I think that that still needs to be dealt with.

Assuming that one could find a surrogate

that was associated with death or other catastrophe and the RCT was feasible, then to try to answer the question, I think that you really probably have to allow changes in the ICS therapy because of the problems that you'd otherwise have with dropout in the study.

Also, it's going to have to be clear in the study and to the population that's being studied that it's reasonable not to step down from LABAs once control is established. Otherwise, the study becomes very difficult to do.

I'm just echoing what many other people around this table have said about the potential difficulty of performing a study if, in the, quote, "real world," people are being stepped off of LABAs quickly and then end up designing a study, where potentially you'd end up doing the same thing. And that ends up with the two or four times larger study population that folks have been talking about when you go from 12 months down to three.

DR. SWENSON: Dr. Fink?

DR. FINK: I would strongly favor the use of

a fixed ICS dosage and no alteration. That is not real world, but to do it real world would severely complicate the study design. You'd have to have more built-in study visits to assess the asthma control and adjust it so that you were not just adjusting asthma control in those patients who complained of symptoms, but you were assessing it on a regular basis.

From a pharmacy standpoint, you would have to have the Advair diskus and the fluticasone diskus in three strengths, blinded for every patient. So it would markedly increase the cost, the pharmacy complexity, and the study design.

If safety is a concern, I would suggest fixed ICS dose and potentially, say, first hospitalization as an end of study point, so that no patient undergoes more than one hospitalization; and, once they have hit that endpoint, they're dropped from the study. That would provide safety of exposure and is an accepted, often used study design.

DR. SWENSON: Dr. Joad?

DR. JOAD: I just want to quickly say the same thing about stepping off the LABA recommendation

by the FDA, that I don't agree with it and I don't think it'll help our study. So that we're all kind of on record, if that's what we think.

I do think in pediatrics, it should be real world. I think that's the only ethical thing to do is to allow them to increase the inhaled corticosteroids, if they need to. But I want to make sure that -- I would like to make sure that it not be done as a way to get around the fact that the Advair 150 is the only does that I can tell that you're planning to use, I think.

You need to be able to include the higher dose inhaled corticosteroids, Advair, in the pediatric studies, because if you try to do it with an extra dose added in, you've got all of the adherence problems that you would otherwise not have if you were using a fixed combination.

Then my last thing is when I said I thought we should do the case control study, I didn't mean we shouldn't do this one. I'd love to do both. I think it would be helpful in children to do both.

DR. SWENSON: Dr. Fleming?

DR. FLEMING: I concur with those who have argued that both ethically and scientifically, to try to understand what is the true real world impact here, I think patients and caregivers should be given the flexibility to manage according to what they optimally believe should be done, guided by carefully drafted protocol guidelines.

This is the approach that's being used in other disease settings, Type II diabetes and the OA/RA PRECISION trial for COX-2s. Obviously, there are multiple interventions that people are going to normally be allowed to take and they should be allowed to take those according to good clinical practices to really be able to answer the real world question.

To me, this was even more reinforced as I was reading through the background information provided by FDA. There were a couple of statements that I found really interesting. One was there's no mechanistic basis for interaction or of the interaction between LABAs and ICS that would explain why, in fact, the ICS presence is removing the LABA excess when they look at the cellular or sub-cellular

levels.

But they did say, among their speculations, might it be that effective bronchodilation could mask symptoms of deteriorating asthma, therefore, delaying the appropriate medical attention and, as a result, allowing for a catastrophic increase in airway obstruction.

I know that's just a theory, but it's a possibility and, in fact, if we legislate against those flexibilities in the non-LABA arm, we may, in fact, be legislating the excess risk that is, in fact, inherent with the use of LABA.

So to get at the real world answer, I think we need to allow this flexibility. Having said this, though, there are issues of concern. It would be problematic in any safety non-inferiority trial, if there are cross-ins or, for that matter, more broadly, excess exposure in the control arm to other agents, it could be harmful on the primary endpoint.

So, for example, if we're trying to see whether the addition of LABA to ICS leads to increased risk against ICS alone and a lot of patients in the

control arm cross into ICS, we're going to dilute away the very signal that we're trying to assess.

So in these types of trials, it's been very important to pre-specify performance standards with targets for achieving those standards and what would be minimally acceptable levels that are monitored by the DMC.

Very quickly, what would those be? One is there should be standards set up for what is the target for the timeliness of enrollment and specifically for getting target populations.

So it's been stated a number of times by Dr. Platts-Mills that it's very important to have, in my words, adequate representation of those high risk setting individuals. I think that should be laid out in advance as a performance standard, indicating who those high risk populations are, to ensure that they are adequately represented, whether they're pediatrics, adolescents, African-Americans, whatever that might be.

Also, standards should be for adequately high risk patients. Then there should be an

indication of what do we envision to be -- I don't want perfect adherence to LABA, I want best real word achievable adherence to LABA. We're not ruling out an excess safety risk if, in the trial, we get a substandard adherence.

Retention, I need an ITT cohort. I want to afford informative missingness and cross-ins. What is the limit, what is an acceptable limit to cross-ins that would be acceptable without diluting? These are all critical to assay sensitivity and these are all issues that really can't be replicated and achieved if we were doing a case control or an observational study. It's one of the advantages of a prospective randomized trial to be able to put these performance standards in place and to follow them.

So my sense is we want best real world achievable. We want something that is flexible that allows patients and caregivers to follow their best judgment. But there are rigors in how this is done in a way to allow interpretability of results that should be identified up front with performance standards that are specified and then carefully monitored throughout

the trial.

DR. SWENSON: Are there any other comments? Dr. Ownby?

DR. OWNBY: I would agree with Dr. Fink that the complications of varying steroid dose in the combinations are going to be tremendous. But if that's not done, I can see all my colleagues blowing the study off and saying, "It's not the way I practice." And if the study isn't going to change practice, I don't think it's worth doing.

DR. SWENSON: Okay. Well, I think we've got quite a split of opinion that issue. We should move on then to question number 4.

Question 4 is, again, on study design issues, whether, in this new design, should the ICS dose remain fixed. Discuss whether the ICS dose should be the same in the treatment arms or whether the ICS monotherapy group should have a higher dose.

It does sort of follow-on with what we were talking about. Dr. D'Angio?

DR. D'ANGIO: I think that this is probably -- well, I view this potentially as a study entry

question, because it depends on when people enter the study. As other speakers have said more eloquently than I can, if you're taking someone who's symptomatic on a particular dose of ICS and give them the opportunity to enter a study in which they'll remain on the same dose or have something added, that may not be a study design that is feasible to enroll into and some people might have questions about the ethics of performing that study.

I just sympathize with the people who are trying to design this. If you take people who are stable and talk about leaving them on what they're stable on or removing something, that has its own difficulty.

The only study design that I've heard that might allow what I think people would probably want, which is same dose of ICS in each group, because otherwise you're comparing at least Gala apples to Empire apples as opposed to the same kind of apples, is to take people who need a step-up in therapy from a low dose ICS and randomize them at that point.

You might then be able to randomize them to

moderate dose ICS plus/minus LABA. That might be an acceptable entry criterion and if that's the case, then you could maintain same dose ICS in both groups. I think other study designs are potentially difficult, because you're asking one or the other group to potentially remain symptomatic.

DR. SWENSON: Dr. Wolfe? I mean, Dr. Joad. Excuse me.

DR. JOAD: I would argue for the same dose ICS to make it much more comparable. I think there probably is something protective about the ICS and if the other group has more ICS, it may be an ICS protective effect rather than a LABA unprotective effect.

I realize I'm arguing, also, for the real life one. So that the ICS alone may end up higher, but I don't think it should set higher.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I mentioned this briefly yesterday, but I had the idea from the FDA briefing materials that they seem to favor people who were stabilized at entry.

Just to follow that through a little bit, that would be the kind of trial that would test out this hypothesis whether or not, as suggested in the FDA new labeling, you could successfully and healthily pull off the LABA.

The other kind of design, though -- and I'm not sure that you can have all kinds of different patients in this study. So Type A is stabilize patients where you're going to put them on one or the other and watch what happens to them.

The other is people - I think we rule out the asymptomatic patients -- but the other are people who have not yet been stabilized on whatever they're on and they get randomized.

The reason I'm raising this is that these questions about fixed dose or not are going to be different in terms of the answers, depending on which of those two kinds of populations. So I think I would like to hear a little discussion on which of those two kinds of populations, already stabilized people or people who have not yet been successfully stabilized on whatever they're on.

DR. SWENSON: Anybody wish to respond to that? Dr. D'Angio?

DR. D'ANGIO: I don't want to be the only one to speak on this, since I'm really echoing what other people have said about this. But I think that a study in which people are asymptomatic and in whom control has been achieved, offering to put them into a study where they have a 50 percent chance of one of the medicines that's in there that has, at least presumptively and in their minds, achieved their control is then removed is potentially a difficult study in which to enroll.

DR. SWENSON: Dr. Krishnan?

DR. KRISHNAN: Sure. I think some of this tracks back to some comments I had made earlier that you're a little bit damned if you do, damned if you don't, in some ways here. There's no easy answer. I'm not sure there is an answer.

If you take somebody asymptomatic, you are going to have a problem if you don't offer that same patient something in addition to what they already are on in the study. So you've got to offer them either

the combination therapy of ICS plus LABA or ICS plus something, higher dose ICS or ICS plus another controller.

That gets very confusing and muddy in terms of then knowing what have you then found in terms of safety signals, because the relative differences in outcomes might not be the LABA, but the package of treatments that now you've compared, and I don't think then we'll be answering the question that we've been asked to pose.

The opposite is also true, which I had mentioned earlier, but I think is worthwhile bringing up again. If you take asymptomatic patients who are now controlled, I think you're going to have a tough time convincing patients to peel off something that got them controlled. It'll affect the feasibility of the study.

DR. SWENSON: Dr. Jenkins?

DR. JENKINS: I'm wondering if people could comment. I've heard a lot of calls for whatever we do should be based on the guidelines, and it seems like if you look at the expert panel report guidelines,

there's a clear point where you could study going from step 2 to step 3.

Step 2 is your own low dose inhaled corticosteroids. If you're failing on that, the guidelines say that step 3 is an either/or. You can either add a LABA to the low dose or you can go up to a mid dose.

So if you're comfortable with the real world approach, there's an ethical place where you could arguably randomize people to what the guidelines currently show as equally good pathways and focus on the safety outcome.

So what do people think about going from step 2 to step 3, randomizing and following for the safety outcomes?

DR. SWENSON: Dr. Krishnan?

DR. KRISHNAN: Sure. I'd like to respond to that directly. So that's exactly the situation that would be potentially doable, but it wouldn't answer the question that we were originally asked, because if you then randomize people to one form of step 2, where you have also increased the dose of ICS, and in the

other group, you've added a LABA, then we're not literally testing the safety signal of LABA, because of all the reasons we've already talked about.

So you would have to then reframe your question. If you reframe your question, then I do see that as actually a real world question that needs to be answered and for which there's not enough evidence. Hence, the guideline recommendation for alternatives.

DR. JENKINS: We had this same debate internally. So I don't think we've settled on whether we're trying to answer the ideal question, which is LABA added to the same dose of steroid versus the real world question of LABA step-up versus steroid step-up, and that's part of what we were hoping to hear here.

We've heard, I think, some voice for the real world approach and if you want to deal with that in an ethical manner, it seems like step 2 to step 3 is a very clear equipoise, where the guidelines say that those are equivalent options that you could be randomized to.

DR. SWENSON: Dr. Redlich?

DR. REDLICH: There are theoretical ways you

could design this, but then there's just the practical reality that just seems, on multiple fronts, that this is not feasible.

Those may be the guidelines, but if you looked at the usage data that we were shown, at least with adults, a very high percentage of the patients were already on a combination therapy. And I think that to recruit those patients and then take away the treatment that is working for them -- I mean, there are multiple obstacles, I think that being one of them. Plus, the additional new data that's come out, such as the BADGER study, showing a benefit of the combination therapy.

DR. JENKINS: You're addressing one of the concerns that we have about the current use of LABAs that maybe has not been as clear. We're concerned that there's a lot of combination therapy initiation.

When we look at the usage patterns for the LABA products, many patients are going directly to combination therapy without any evidence that they've previously been on the ICS. So that's one of the concerns we were trying to address in the label

principles is go through the stepwise care before you jump to the dual therapy.

The labeling forever has had the option to go to dual therapy in situations where it's appropriate. We're, quite honestly, concerned that the marketing pressures are leading to a lot of people going directly to dual therapy.

We're also concerned that in that environment, a lot of people are then stuck on dual therapy who may not need dual therapy, and that goes to our question about carefully considering whether you need to be on the LABA chronically.

We've heard a lot of the feedback about the step-down approach that we talked about in our announcement and we'll take that back and consider that.

I would have to press a little bit, though, that being on the LABA shouldn't be a lifetime prescription. There should be some clinical judgment that you decide it's needed, but later I'm going to decide that maybe it's not needed.

We heard, for example, about seasonality.

Some patients have worse symptoms during season. So maybe those patients get a LABA added to their steroid during a season. But should they stay on it forever?

So we're trying to capture both principles, delay initiation of LABA until you've failed the ICS therapy, which is exactly what the guidelines say. You can debate how far you have to wait until you've failed ICS. The guidelines currently say at low dose. We suggested maybe mid dose.

But we are very concerned about people jumping directly to dual therapy and then staying on it indefinitely, and we're trying to communicate -- delay therapy until it's clearly indicated in that individual patient and then it shouldn't be a presumption that you'll be on it forever.

Given that asthma is an intermittent, variable disease, there may be situations where you can step back, and stepping back is a principle that's outlined in the guidelines.

So I'll stop.

DR. REDLICH: I think everyone agrees with that. It's just that designing a study to study the

effect on mortality is different than designing a study for how one would step down, and I think everyone agrees that there needs to be more data on how to step down.

DR. JENKINS: Yes. But what I proposed as a study design didn't include stepping down.

DR. KRISHNAN: If I could address that, also. So the GOAL study involved stepped care, which we talked about. They essentially compared adding a LABA versus increasing doses of ICS, and there's various permutations around it, but essentially compares with what you're talking about.

Also, we have the BADGER study. Dr. Lemanske mentioned that that was just recently published. It also talks about stepping up therapy. And in both those situations, for the efficacy outcomes that were measured, as you know, the combination therapy won compared to other approaches.

So that's why we have to decide what is the question. If the question, again, is back to safety, I guess it's still on the table, but that would be a very different question than originally we had been

brought in to discuss. But there are no safety data that would address the two alternatives of step-ups from step 2 to step 3.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: Thank you. I was going to make the comment earlier that I continue to be a little concerned about what to do with the stable asymptomatic patient. And I would agree with Dr. D'Angio in that this should perhaps be an entry criteria and that the patient has to have some degree of compromise or you would then do something, rather than just taking patients that are in their stable state and randomizing them or observing them or continuing the study with them.

DR. SWENSON: Dr. Fink?

DR. FINK: The briefing document had given study designs that didn't involve a run-in period and it probably shouldn't be a run-in period. But I think the only way you could really adequately address this issue would be to enroll all comers and then after enrollment, you actually step everyone down to ICS only at medium dose, and then, depending on those who

are symptomatic, you then randomize.

If you did that, you would get some data on how many patients are currently on ICS/LABA combinations that successfully stepped down to ICS alone and don't need the combination, and you would then have clear equipoise for stepping up those who were inadequately controlled on ICS alone.

But that does clearly complicate study design, because it would be enrollment, then run-in post-enrollment on a fixed level ICS dose, then randomization, if they were symptomatic. But that would be probably the only design that would address your question adequately and still allow adequate numbers.

If we only take step 2 to step 3 new patients, it's going to take forever to enroll.

DR. SWENSON: Dr. Greene?

DR. GREENE: Thank you. Most of my comments have already been raised, but I would echo what Dr. Fink said. I think that the relevant question, practically, is that step 2 to step 3 question about where do we go with this and is it really the safest

thing to use a LABA as opposed to going to a higher dose of corticosteroid; but, of course, it complicates the feasibility issues.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: Dr. Jenkins used the term "we are very concerned" and that comes through in the proposed new labeling guidelines, but it's not clear to me why you're so very concerned.

Clearly, you're not proposing similar regulations for montelukast. Montelukast is a drug that's probably being prescribed to a lot of people for whom it does nothing and working beautifully in others, and we have great trouble sorting out which is which.

So on the grounds of what you just described, that would be an equally relevant thing, instead of which the language uses "fear of catastrophic outcome, death," all these things, and this seems to be entirely based on a completely faulty meta-analysis by Salpeter, which doesn't fit with national experience or personal experience of physicians. So you're not going to get anywhere with

that.

The catastrophic outcomes -- so that now, we're left with a really ridiculous situation. That is that the FDA is telling us that this drug is dangerous, everyone should be warned they're going to die.

Every physician treating this disease -- most of them do not agree with you. Very, very few agree with you. And furthermore, we have the television telling us every night that you're going to be wonderful if you take this drug.

This is a ridiculous situation, absolutely insane. And it's typical American, I must admit.

[Laughter.]

DR. SWENSON: Dr. Ownby? Oh, I'm sorry. Finish, Dr. Platts-Mills.

DR. PLATTS-MILLS: Every previous epidemic of asthma has had a rise in asthma mortality. This so-called disaster, which Dr. Graham, I think, believes is a real disaster, is associated with a massive rise, you've got 6 million patients taking combination therapy and a progressive decline not only

in asthma deaths, but a progressive decline in hospitalizations.

I have heard no explanation from the FDA about why they think that this drug, which is being taken by 6 million people, has this odds ratio of 3 for death, and yet the mortality rate for asthma nationally is going down.

Do you doubt the national statistics on death from asthma? I mean, you could, if you like, but I think you'd be on very poor ground.

DR. SWENSON: Dr. Chowdhury?

DR. CHOWDHURY: Maybe I can step in here and put some of my parts here, two aspects, one on the issue that you're touching on, and, second, going back on the clinical trial design issue.

If you look at the asthma guidelines, which we are discussing here, I don't want to go too much into that, if you look at the stepwise care, there is a stepwise going up and stepwise going down.

On the stepwise going up, if you look at the criteria for going up, I'm just reading from the guidelines here, use of short-acting beta-agonist over

2 days a week, not for EIB, indicates inadequate control and the need to step-up treatment.

So a patient using albuterol, for example, for 3 days needs to step up and the step up then is a lower acting beta-agonist. So a patient taking albuterol 1 day a week, second day a week, third day a week, is stepped up to a beta-agonist, long-acting, which is now 14 times a week.

So that is the dilemma that one has that these current guidelines -- although the albuterol is a marker of asthma control, but if you interpret that, it actually introduces a long-acting beta-agonist very early on. And for overall beta-agonist use, you're going up tremendously from using 3 times a week, which is only three doses, to 7 days a week.

The other thing I wanted to point out, which was touched on earlier, that these are, for long-acting beta-agonist class effects, not necessarily without an association. With salmeterol, we have the data, which we talked about multiple times here. But formoterol, small trials, actually had a short effect.

If you look at beta-agonists as a whole, I

think everybody understands that older beta-agonists, fenoterol was covered multiple times, is an effect which we all agree on. But if you look at albuterol, there are two clear trials, that were touched upon earlier, which were negative, and albuterol does not have a boxed warning, whereas salmeterol and formoterol have the warning. So there's a distinction to be acknowledged.

We're talking multiple times about stepping up and stepping down. The one thing that's coming back is once the patient is in control, why should they step down. The exact asthma treatment guidelines say step down, if possible. So stepping down is already in the guidelines. So stepping down is there.

So I'm not sure why stepping down is not something which would be an option for usual care. Thank you.

DR. PLATTS-MILLS: Because that's not how we practice and that's the problem. And if you see a real signal, do you see a signal of increasing hospitalization of some community in which combination therapy is being used on a reasonable scale? Because

I'm not aware of such data.

I debated Bill Busse (ph) about the guidelines two weeks ago at our national meeting and he presented the data that hospitalization is going down in this country and we have 6 million patients taking combination therapy.

So why are you so concerned? I'm well aware of the albuterol. I'm well aware of the isoprenaline. I was trained in the middle of it. The fenoterol I'm well aware of, because Julian Crane is a personal friend and I understand exactly how that was worked out. And I've known about salmeterol since the first trials in England. It was quite clear that salmeterol was a problem.

Once it got released -- not in the original trial, but once it got released to the public, there was this signal. But we're not getting that signal with combination therapy and you haven't presented in data, and Salpeter muddies the water horribly, because she then mixes straight salmeterol with the combination and the signal is from the salmeterol or formoterol, not from combination therapy.

So there's no justification for using all this terribly inflammatory language in the proposed new labeling.

DR. CHOWDHURY: I think we should focus back on the clinical trials. We have been going back and forth, but, again, to point out that -- I mean, you yourself is saying that asthma death is actually increasing in some segment of the U.S. population.

So overall, there's a trend, but not necessarily it is already gone. Again, going down in the trend is a very positive thing, but that does is not necessarily an idea situation.

If you look at some of the countries, like, I believe, Finland has essentially no asthma death in the whole country. So going down on the trend is a very positive thing, some Northern European countries.

DR. PLATTS-MILLS: Yes. But they don't have any dust mites and the death rate has cursed primarily New Zealand, high dust mite, incredible levels of sensitization, and that's where the deaths occur. England, high rates of mite sensitization, and that's where the death occur.

The United States, inner city, high rates of exposure, Morgan and Rosentreich, excellent data showing that that is a major risk factor, that's where the deaths are occurring. And unless you address those issues, this is pointless.

DR. SWENSON: Dr. Jenkins?

DR. JENKINS: This is just a good case example to illustrate. If you've already concluded that there is no increased risk of these serious catastrophic events with combination therapy, then you see no need to be worried about combination therapy.

If, on the other hand, you haven't reached those conclusions, then you may still be concerned about combination therapy. We have not reached the conclusion that the risk that was seen with salmeterol is not present at some level in combination therapy.

That's why we're here asking you about doing additional studies to try to better quantify that risk. Dr. Platts-Mills, you have clearly concluded that there's no risk. So in your mind, there's absolutely no value in warning or restricting the use of the products, because you've concluded there's no

risk of the combination. That's not a universally held view.

DR. PLATTS-MILLS: But you're proposing changing the language on the --

DR. SWENSON: I think this argument -- Dr. Platts-Mills?

DR. PLATTS-MILLS: -- before we do the trial.

DR. JENKINS: The label has had a boxed warning for this effect for this effect for years. We're proposing to change some language. We've already said, based on the feedback we've heard today, we will consider that.

We haven't finalized any labeling. We've heard your concerns and we've said that we would address those. But the boxed warning has been on the product for years.

DR. SWENSON: Let's move on then to Dr. Ownby. You have a comment?

DR. OWNBY: How can I follow this discussion?

[Laughter.]

DR. OWNBY: I was going to try to get back to the study design. And I would agree with Dr. Jenkins that the step-up from step 2 to step 3 is an appropriate place where you could start a study of this nature.

My concern is, and I know many of my colleagues have a lot more experience enrolling people in clinical trials, in my office, that is a tiny fraction of the patients I see and I think it would be very unfeasible to enroll at that point.

Where I think you might get a few more patients, though, if you consider step 3 and you offer to enroll people to consider the relative risk of the combination product versus their inhaled steroid and the risks that may come with that, because I think that's where we're trying to trade equipoise, is the long-term risk of a certain dose of steroid versus presumably a smaller dose of steroid with a long-acting beta-agonist. But even that is going to, I think, create a lot of problems, because, again, we're sub-segmenting all these individuals with asthma, and that makes enrollment a big challenge.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: This is a little bit like the discussion that occurred in December '08, but I think that the data that FDA presented on current use sort of emphasizes this.

As Dr. Jenkins said, there are a number of people who have gone to combined use without -- and have missed the step before that, and that is a serious problem. It is probably that as much as anything, combined with whatever unresolved risk there is from these drugs, to get the FDA to make these guidelines.

So would it be possible it identify a group of people that are taking the combined drug, but, in fact, went there missing the step before that? It would seem that there are a large group of such people. We know that from FDA's data presentation. And then take this group of people who are already presumably doing okay on the combined drug and randomizing to just continue doing exactly what they're doing or to go just to inhaled corticosteroids.

It seems like that is a huge problem. You've confirmed FDA's previous concerns about that, and I think that there, you'd have a different -- still some ethical questions, but it would be very different than the step-up kind of thing to someone.

So anyway, I just wonder how large that group of people is. There must be some estimates based on FDA's data and whether one might consider that as a trial design.

DR. JENKINS: Are you suggesting that they would be randomized to staying on the combination or going to the ICS at the same dose that they are on in the combination or stepping up their ICS dose?

DR. WOLFE: That's up for discussion, just as it was before. But overall, that would be the design. If they're already doing well and didn't have a chance to see whether they would do well on just the ICS alone, which is almost by definition, which means stepping up, leaping over the step 2 and going up to the combined, that may be an interesting question to answer.

DR. JENKINS: It sounds somehow similar to

what Dr. Fink was suggesting of bringing people in and having a run-in period and then randomizing based on the run-in period.

DR. WOLFE: I'm just suggesting something simpler than the run-in, because you should be able to identify, at least most of the time, whether or not the people stepped up to combined therapy and missed out on just the ICS step. That's all. Same idea, though, generally.

DR. SWENSON: Dr. Joad?

DR. JOAD: The guidelines allow you to go straight to combined therapy if you have severe enough asthma, and it's not fair to a patient to make them start at a step and then go to the next step. I mean, that's not their recommendation and I wouldn't do it clinically.

If somebody really has bad asthma and they're not controlled, you would put them on an appropriate step and then you move up and down as possible, and that can mean taking them off. But there's nothing about the guidelines that says you have to start at step 1 and 2 and 3, and that would

really be a disservice. You would also get really, in my opinion, poor adherence from the patients, because why would they hang with you while you mess around going up steps that aren't helping them.

DR. WOLFE: Just a 10-second response, which is the severe asthma, that may be true. But, again, from what was presented yesterday and what else there is available, a lot of these people that are put on the combined product do not have severe asthma. They had some asthma and they just sort of started them off on that, literally, as their first asthma drug. That's what I'm talking about.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I'd like to echo Dr. Wolfe's point. I'm not an asthma clinician, so I'd have to leave the asthma clinicians to tell us what proportion of people really probably started on a combined therapy without severe indications that their asthma was severe.

But I think, trying to pull together the groups that I've heard, that it might be reasonable to enroll in a study where the dose of ICS is the same

between arms and LABA is in one arm.

One group might be a group of people who stepped up to combined therapy without having severe asthma, who never had single-agent therapy before they stepped up. Another group might be the group that need -- that group going from step 2 to step 3, small, I gather, for whom the additional risk of going from low dose to mid dose steroid might be reasonable, if you want to keep the steroid dose the same in the two groups.

Then somebody might be able to imagine a group who's been stable on combined therapy for long enough that it was reasonable to consider stepping them down. I don't know how long long enough is. It's probably not somebody who has just achieved control. But there might be a group that had been on therapy for long enough that a clinician would consider stepping them down, and that might be another group.

It gives you a hodgepodge of people coming into the study, but all of those are groups that it might be relatively easier to enroll.

DR. SWENSON: Dr. Chai of the FDA, have you got something to say to this?

DR. CHAI: Yes. I just wanted to clarify some of the comments made by Dr. Wolfe. I was just wondering if you are -- may I refer to a slide from my presentation, to slide 6 from the drug utilization presentation?

Unfortunately, we didn't do a time series analysis of combination products. What was presented are total dispensed prescriptions. Is this what you were referring to as to when you were making your comments about people skipping the step?

DR. WOLFE: No. I think there were other data on the issue of whether or not people has started out with a combined product as opposed to --

DR. CHAI: Okay. That was in the further analysis section, slides --

DR. WOLFE: I don't remember the number of the slide.

DR. CHAI: Slide 12. This was actually an analysis for salmeterol alone and the time series analysis of salmeterol alone. So it doesn't actually

discuss combination products. I just wanted to clarify that. Thank you.

DR. SWENSON: All right. I think we should move on then to the next question, number 5, which then gets to the question of length of trial and treatment to address the safety concern both in adolescents, adults, and the pediatric population.

So if we could have some comments on length of trial, as to whether 6 versus 12 or even here posed 3 months.

Dr. Fleming?

DR. FLEMING: Actually, I didn't get to offer a comment on question 4. Could I still do that?

DR. SWENSON: Yes. Make it short, and you will.

DR. FLEMING: I'll be very short. And the first part of the comment is just to endorse what several have said, and, that is, I think in this setting, it's a particularly key setting to, as best as we can, represent the step-up scenario, such as the step 2 to step 3.

I just want to reiterate, in my view, if

there's a difference on the average level of exposure to ICS in the two arms, that is not problematic. That's really a secondary endpoint.

The second very quick comment is relative to a lot of the discussion that went on. Broad clinical opinion can emerge in settings when we don't have reliable evidence-based justification, and this is particularly possible in settings where there could be catastrophic events that do occur with background therapy, even without the intervention in question.

Just to five one example, post-MI, if you have an arrhythmia, half a million patients a year were using encainide/flecainide because of the strongly held belief that when you suppress arrhythmias, that's going to reduce sudden death.

Yet, a study was able to be mounted involving 2,000 people randomized to placebo, in spite of that broadly held opinion that, in fact, encainide/flecainide should be given. And as many of you know, that study showed that it didn't provide benefit; in fact, it tripled the death rate.

So I guess my sense is when there's a

discordance between TV ads and the FDA's views, FDA is not always wrong.

[Laughter.]

DR. SWENSON: I'm sure that's a welcome thought from at least one quarter of the room. All right. We'll move now then to question 5 about duration of trial length here, and questions. I think I see Dr. Cnaan.

DR. CNAAN: Yes. In particular, in the pediatrics, I would propose that we need the 12-month, not the 6-month, for two reasons. One is the issue of seasonality, which may be relevant in the adults, too, but is relevant in the pediatrics; and, two, because we are saying that, secondarily, we are going to want some efficacy things, like missed school days and so forth, if you do it as a 6-month study in pediatrics, you would have problems in that component.

So it would also make the estimates that Dr. Fleming provided earlier be half the size if you do the 1-year study. So for all of those reasons, that's my suggestion in pediatrics.

DR. SWENSON: Dr. Fink?

DR. FINK: I would echo those comments in terms of seasonality, but, also, just say I think, in general, conducting clinical trials, it is far easier to retain people for a year. It gets progressively harder after a year, but much easier to retain people for a year than to recruit twice the number of subjects.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I want to echo the thought that a 12-month study is probably reasonable. One of the arguments that was posed yesterday for a shorter study would be the potential risks, if there were risks to subjects, that they be exposed to those risks for longer if they were in a 12-month study than if they were in a 3-month study.

That assumes, A, that there are risks, which is what we're studying, we don't know the answer to that question, but I'm not -- maybe some of the ethicists can help me here. I don't know whether it's better ethically to expose one person to risk for 12 months or to expose four people to risk for 3 months each. Provided that there's not a strong -- provided

that continued use of LABA is not being strongly discouraged by regulation or labeling or something else, I think that it's potentially more reasonable to include one person for 12 months because of all of the reasons that other people have already given.

DR. PLATTS-MILLS: Can I just say a word about the seasonal exacerbations? It is a very big phenomenon in asthma, the seasonal rise in September, which is seen internationally, and it's become very interesting, because the Inner City Asthma Consortium has reported at our annual meeting that anti-IgE removes the full epidemic of asthma, so that we're beginning to understand it.

So that if you don't involve that, you won't -- [off microphone.]

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I think that the seasonal arguments, aside from just the known seasonal allergens, are very persuasive. I think that from an ethical perspective, I don't think that there is a huge difference, particularly if there is a very aggressive, active data safety monitoring board. So

if a signal comes up at 3 months or 6 months that occurs, you can stop the study. So I think maybe we should ask if there are people that disagree with the 12 months, just to expedite the decision.

DR. SWENSON: It does seem we have some unanimity on this, but I should open it up for anybody who disagrees.

Dr. Joad?

DR. JOAD: Actually, I don't disagree, but I think it has to go along with allowing extra inhaled corticosteroids. There has to be. You can't put somebody on something for 12 months that may give them suboptimal control, in my opinion. They have to have something else; maybe not that, but I'd prefer that.

DR. PLATTS-MILLS: Could I just describe how we do that, how I do it? I say to a patient to step down. All right. So you step down to a slightly lower dose and you say keep the other medicine in hand let's go down for two weeks. If you feel that this is not working, you're going to have to go back on the previous dose.

That is, you have a lot of personal choice

in how they handle it, so that you don't create a fear that they're going to exacerbate and not have something they can do about it. That's extremely difficult to build into a control trial.

DR. SWENSON: Any other thoughts on the length of trial? Dr. Rosenthal?

DR. ROSENTHAL: Just a quick one. I agree with the potential favorable impact of a 12-month trial with regard to the seasonality issue.

But the other thing that I'd say is that we do -- it seems like we do have some data on the timing of the events of interest from some of the previous clinical trials. And so if all the events are happening a week into therapy, that might strength an argument for a shorter duration and more people as opposed to -- if none of the events are happening between months 6 and 12, then that may not give us information out there.

So I would just use the available data to try and inform this question, as well as the theoretical principles that are being discussed.

DR. SWENSON: All right. We can move on to

the sixth question, and that is regarding the time frame under which these potential studies might be done and length of time to complete in the face of possibly evolving new therapies and practicalities of maintaining enrollment.

So I think we have the idea that has been bounced around as 5 years, but we should open it up to other discussion.

Dr. Wolfe?

DR. WOLFE: I agree with those who said that if we're going to do a trial, that 5 years should be the outer limit, if it can be done more quickly. Otherwise, you sort of get the news and everything else sort of surpasses the ability to do the study.

I think 5 years is a reasonable amount of time. Again, if there are some people that think it needs to be longer -- some of the projections, which I think were questionable in terms of their basis, that it would take 10 or 15 or 20 or 30 years, based on these tiny allowances of additional risk, are just that. I think that 5 years is a perfectly reasonable period of time.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: Could I suggest that in order to enroll the minority population, one of the things that could be done would be to try and involve the Inner City Asthma Consortium.

The Inner City Asthma Consortium and, particularly, Herman Mitchell, who is the main statistician, have enormous experience at enrolling patients in this population and handling them, and I think it would be a great message from the FDA or from us that the NIH should try and focus on these issues.

DR. SWENSON: Okay. Well, then our last question here is given that the data from the SMART study suggested a higher safety signal in African-Americans and national statistics indicate a higher rate of serious asthma outcomes in the African-American population, a representative number of African-Americans are proposed for inclusion in the U.S. study sites.

Discuss the challenges for obtaining meaningful information from this subgroup and analysis in a proposed study and possible means to address

that.

Dr. Joad?

DR. JOAD: Well, I would hope it would be enriched, not just representative; that there would be more than is -- the proportion of African-Americans in the study would be more than the proportion that are in the population, in general.

DR. SWENSON: Allowing for possibly a stronger signal.

DR. JOAD: That would help, yes, a subgroup analysis, and we're specifically interested in that group. And then all the many comments that have been made about how to enroll I think are excellent ones.

DR. SWENSON: Dr. Mouton?

DR. MOUTON: I agree. I think it's essential that a subgroup analysis be planned and the subgroup population be enriched. My experience with clinical trials that have done this, using the Historically Black Colleges and Universities. They're spread all over the country and there's been encouragement to do partnerships through the NIH with them for research I think would be one solution;

obviously, using the community groups, particularly, reaching out to churches and other community-based organizations.

That, again, was encouraged by NIH through its CTSA award. All of those are strategies that could be used. Practice-based research networks are springing up in many of the urban areas. All of those opportunities, as well as community health centers, all those are ready-made networks that could be tapped into trying to recruit the population.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: The ways that I can think to try to address this problem, to add to what people have already said, and I'm sure other people will say, are to use all the means that people have discussed to try to enrich the populations.

But we have to recognize that that still won't be the entire sample size. So that we're stuck with subgroups that will be more difficult to analyze. Other ways to try potentially to mine for signal in that group would be to combine outcomes among studies, pre-planned, and to consider a specific case control

for catastrophic events in a population that, unfortunately, the cases are already highly enriched for minority populations, because people who die from asthma are disproportionately coming from minorities.

So that a case control study would be another way to try to get at the risk factors in minority populations.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: The language of subgroup analyses in the context of the clinical trial seems to imply that at the end of the study, we will compare, within the subgroup, between the treatment groups.

I would maintain that since being African-American seems to be a predictor factor for a higher rate, that up front in the design, you should stratify by being African-American as a stratification factor and randomized within that so that, at the end of the day, you would get the meaningful comparisons within the subgroup.

DR. SWENSON: Dr. Wolfe?

DR. D'ANGIO: Can I? Sorry. I think, however, there still remains the risk there that the

power in the group won't be as high and that it's reasonable to think of other ways to try to get at the signal besides stratification, because the power within each subgroup won't be as high as we'd like.

DR. CNAAN: This is in addition to the various enriching methods, all of the comments, which I agree with, before. But I'm saying up front at the design, just make sure that for all of that effort, you also get something at the end.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I think this is implied in the way the question the worded, but just to make it crystal clear. It is not just being African-American. As pointed out by several people, it is particularly people in the inner city and in the lower socioeconomic classes, where the risk is even higher.

So that rather than simply say we want to get X proportion out of proportion to the general population of African-Americans, within that, we need to make sure that there is a good enough representation of people who are at the highest risk amongst the African-Americans. I think that can be

done by the nature of the recruiting suggestions that have been made on that issue. I think we need to be very clear about that, though.

DR. SWENSON: Dr. Ownby?

DR. OWNBY: I have a concern about this discussion, if we talk about stratification or enrichment, that, in the end, we will not see a signal in the entire group, but there will be a suggestive signal in a subpopulation and that will start this whole process over again.

If we really think this is important, you have to power the study for at least a signal in the African-Americans as a unique group and whether you do that as individual studies or in part of a combination. But otherwise, I see us walking into another tar baby on this one.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: I would like to support Dr. D'Angio and Dr. Camargo. I think the study that you really need to do is a case control study in the inner city. I don't think you can do a controlled trial in the inner city. Enrollment will never match

what you want and compliance will never match what you want.

What we really need to understand is the causes of asthma death in the inner city and really design the study to find out what the causes of death are, and if combination therapy or LABA is part of that, so let's find out.

I think if we apply any of these studies to an affluent Caucasian population that will comply with control trials, at the end of 5 years, you're not going to know anything.

DR. SWENSON: Dr. Fleming?

DR. FLEMING: I had noted earlier the importance in these safety studies, non-inferiority, where you're trying to rule out excess risk, that it's extremely important to set up in advance a number of performance standards.

One of these performance standards that I alluded to earlier was timely enrollment of the target population, where there are two elements that I think of as being especially important in target populations, those that have a high risk of events and

those in whom you have a suspicion for the highest relative risk, the highest adverse risk.

We've heard the high risk of event scenarios apply to, in particular, possibly, inner city and those of lower socioeconomic classes, and, certainly, suspected to have a higher relative risk and would include, among others, the African-American cohort.

In SMART, the overall asthma-related death rate yielded 16 events, I believe it was, 13 against 3. I believe approximately 18 percent in SMART were African-American. They contributed more than half the events. I think it was 8 against 1 in that sub-cohort. So they contributed at least half the events, with only 18 percent of the people.

It's actually numbers of events that provides the power to be able to understand excess. So ideally, we would love to not only understand globally what the effect is, but to understand it exactly by the regimen, exactly by whether it's step-up/step-down, exactly by the risk categories, and that level of insight will always escape us.

What we need to try to do is make the best

assessment we can and on these rare events that are so extremely important, we're going to be forced to do some pooling. But we clearly need to identify up front which of those groups that need enrichment; and, that's not to say that when we do that, that we're going to have 70 percent of the study that are African-Americans.

But ensuring that we have at least 18 percent, in fact, working toward achieving a somewhat higher level, 33 percent or something at that level, is still going to give us a very large amount of information in a generalized setting, but, also, it's going to increase our sensitivity in those patients for which there is the greatest need to understand benefit-to-risk. And it will yield more events and the more events we have, the greater the power we will have.

It's extremely important to think these issues out in advance, establish performance standards for what is your target level of representation, what's minimally acceptable, and have close data monitoring committee review of those as the study is

emerging to be able to have a much greater sense of likelihood that we're going to have the representation that we need to get the most insightful answer we can get.

DR. PLATTS-MILLS: I'm sorry. Can I ask the companies to address what Dr. Fleming has just said? That is, if you have a study of 24,000 and you're proposing that 33 percent should come from the inner city, could the companies answer what they think would be the challenges of enrolling 8,000 patients from the inner city?

DR. FLEMING: Well, as they answer that, the basis for my comment was looking at representation of the population and looking at what was achieved by SMART. It was 18 percent. The 33 is not a rigid number. I want that to be specified by the team after a great deal of thought.

My point, though, is it would make sense, as someone has already indicated, to actually try to achieve, for your high risk and for those cohorts that you expect to potentially have the greatest concern about excess risk, to, if anything, not just have

proportionate representation, but some level of over-representation. I don't know if it's 33 percent, but something in excess of 18 percent.

DR. SWENSON: Let me ask the sponsors -- I know this is sort of coming out of the blue -- if you could just spend maybe a minute each on what you think might be the concerns and feasibility.

This is Dr. Knobil.

DR. KNOBIL: Well, I mentioned earlier that with the results -- I'm sorry. Kate Knobil, GSK. I mentioned earlier that because of the results of SMART, we did a study of only African-Americans to look at exacerbation rates. I don't know if we can put up the slide again. But there were about 500 patients in that study and that study took 13 months to enroll, to find 500 patients, fewer than 500 patients.

So you can imagine that trying to find 8,000 patients would be a challenge in such a study. So I think that Dr. Camargo would also like to talk about the mortality rates in African-Americans, as well, because I think there's been some statements about

that, rates are rising, when, in fact, they may not be.

DR. CAMARGO: Just literally, 30 seconds. Carlos Camargo, Mass General Hospital. I just heard several times people refer to the unique burden in African-American, and I raised the Hispanic community, and that is certainly there.

What people have focused on is how the death rate is dropping faster in white Americans than it is in people of color. I don't want to disabuse you of this idea that somehow it's rising among African-Americans, because that's just not true. Hispanics, African-Americans, all groups have experienced a reduction in asthma mortality over the last decade, and the data are from the CDC. You can find it on the American Lung Association website. It's crystal clear.

DR. SWENSON: Dr. Bonuccelli, AstraZeneca?

DR. BONUCCELLI: We've actually been working on this challenge of minority recruitment for years, probably for at least the last 5 years or longer, and have found it quite difficult. The infrastructure

doesn't exist. The patients don't have standard physician care. And we had partnerships with the NMA to try to achieve that, as well.

What we do have, from an experience perspective, is I told you we have a 720-patient African-American 1-year study that is closing this year. It took us 22 months to recruit those 720 patients.

DR. SWENSON: Dr. Pascoe?

MR. PASCOE: I'd echo the previous comments. I think we're actually framing the question without accurate numbers, and I don't think we've asked the question appropriately, whether we're interested in inner city or we're interested in African-American.

I would make a plea that if we're interested in African-American, we extend that to people of African extraction, wherever they are, or if we're interested in inner city Americans, then we direct to that. Then the next step would be to conduct some real feasibility in conjunction with the groups that have been suggested. I think diving off blind now would be potentially catastrophic to anything like a

5-year timeline.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: Very briefly. The issue of having subpopulations, including the African-Americans, as well as the Puerto Rican/Hispanic community, this is a golden opportunity for us to look at the beta receptor polymorphisms and the genetic basis of asthma, and that absolutely has to be part of the study.

DR. SWENSON: Dr. Kramer?

DR. KRAMER: Just quickly. I was, again, a little concerned about the assumption that a few people seemed to make that if we did the observational study here, that we would be able to deal with the discussion in African-Americans better. But if you look at the databases that are included in the slide, many of those do not represent a large proportion of African-Americans and certainly not inner city people who don't have health insurance coverage.

So, yes, Medicaid would and the VA would, but Innogenetics, the HMO Research Network, WellPoint, these are not highly enriched populations for what

you're saying you're interested in looking at.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: I'll echo what other people said about the difficulties of the design here, but I'll echo what Dr. Ownby said about the risks of launching off into this kind of study without being clear about what the question is.

I think that the disproportionate risk of death, although it's falling in inner city communities, is still there and if we have a question about that, the study should be designed so that, if it's at all possible, that question can be answered as opposed to a study design where we hope we can answer it and find out that it's inadequately powered.

DR. SWENSON: Dr. Mouton?

DR. MOUTON: I guess maybe because I am who I am, my experience in several clinical trials, including some of the largest trials NIH has ever done, has been if you have a concerted effort to recruit an African-American community, you can make your targets. And I made them at Newark, New Jersey; I've made it with Hispanic populations in San Antonio,

as well as Howard.

So part of me is saying, okay, it may be a problem for folks who are not making a concerted effort, but if you make a concerted effort, you can achieve these numbers. And this is clear in the Women's Health Initiative, it's clear in the study of women across the nation, it was clear in the Hispanic established populations of the elderly, all studies which I participated in, and we made our targets.

So I think if you do make a concerted effort, there may be some differences in terms of how you have to plan your recruitment, you can make them. So I just wanted to leave us with that thought.

DR. SWENSON: Well, at this stage, we're going to depart just a little bit from the plan here. We finished the questions, but there has been some suggestion among panel members that we take something of a straw vote to further guide the FDA.

The question that I pose, and it's an opinion that I would like you to just say yes, no, or you're welcome to abstain, but the question would be, can you provide your opinion as to whether a

randomized control study can be profitably undertaken, with all the discussions we've had, or should some other approaches be used; for instance, we've heard case control.

DR. WOLFE: Would it be instead or in addition, either/or?

DR. SWENSON: You can add either/or, if you wish. I would ask that you don't put too many caveats on this. It's just a global sense for the FDA.

DR. KRAMER: Could you state what the purpose of the study will be?

DR. SWENSON: I think, for fairness sake and to proceed, that we ought to make it on the composite events, because in a sense, this might be practical. But, again, we could dice this down into numerous, numerous questions, and I think the FDA would just like to hear some guiding sense of where they think they should move.

So, Dr. Hubbard, can we have your opinion, if you wish to say so?

DR. HUBBARD: This would be a first for me, since I'm generally a nonvoting member.

DR. SWENSON: Well, you're on the panel, so you may provide an opinion.

DR. HUBBARD: If the question is a composite endpoint rather than just deaths and intubations, I believe that a randomized trial could be done. I suspect that it's going to be very challenging.

I think that meeting a 5-year timetable will be a shared commitment not just amongst the sponsors, but amongst a lot of other people, too, including the agency and the professional societies who have the investigators in their ranks.

So it will be possible, but I think it will be very challenging to do.

DR. SWENSON: Okay. Dr. Morrato?

DR. MORRATO: To keep it short, I agree with that. I would like to still see, though, the case control design in order to investigate further the deaths, and I think it can be informative to help us understand causality, but what factors are also driving it. Thank you.

DR. SWENSON: Dr. Cnaan?

DR. CNAAN: If feasible within a 5-year

outcome, I think it should be done. I think it's absolutely essential that the outcome definitions be uniform across sponsors so that we don't end up with something that's not interpretable. And I would support doing the case control study, regardless of the clinical trial.

DR. SWENSON: Dr. Krishnan?

DR. KRISHNAN: I think the primary outcome of interest, as we've discussed, is respiratory-related near fatal or fatal events. And with that as a composite outcome, I would strongly urge us to adopt a case control study, a nested case control study. I do not think a randomized clinical trial is feasible within the time frame in which we're looking for information.

DR. SWENSON: Dr. Mouton?

DR. MOUTON: I would suggest that a composite endpoint of mechanical ventilation and death be used and that we do a case control study and if that shows an increased signal, then we go to a randomized control trial to confirm it.

DR. SWENSON: Dr. Redlich?

DR. REDLICH: I would agree with Dr. Krishnan that if the primary concern is mortality, that an observational case control study would be preferred. If the concern or the interests are how to optimize treatment and stepping up and stepping down, then that would be an alternate study design.

DR. SWENSON: Dr. Platts-Mills?

DR. PLATTS-MILLS: I think if we wish to address the FDA's concern, which is apparent in the language they're proposing, then a randomized, double-blind, controlled trial is most unlikely to answer that question.

DR. SWENSON: Dr. D'Angio?

DR. D'ANGIO: A randomized control trial would potentially be able to reach the information about the combined outcome that FDA has proposed, but I think the question is whether that's what FDA wants to be looking at, which is death, intubation, and hospitalization is really a reasonable outcome.

I think that it's potentially feasible to do a randomized control trial that uses an outcome that's more restricted, but someone would have to run the

numbers for that. And if the outcome of interest is death or mechanical ventilation alone, then probably a randomized control trial would not be feasible for that.

It doesn't mean the randomized control trial isn't reasonable to look at the overall question, but it wouldn't answer the question about death and mechanical ventilation, and that should probably be answered through a case control mechanism.

DR. SWENSON: Dr. Wolfe?

DR. WOLFE: I think that for all the things that have been studied the last couple of years, a randomized control trial, with the expansion, as begun to be discussed today, from just death and intubation to noninvasive ventilation and so forth, is really the only way to answer this question.

I would say that a randomized control trial would also be the better way, if you also broaden it to include hospitalization. So I would favor of that in either of those two scenarios in terms of the primary outcome.

DR. SWENSON: Dr. Fink?

DR. FINK: I would favor a randomized controlled trial using the composite endpoint, because I think the case control study of deaths may very well not show a signal and then we're still left with the more important question of is there a risk to LABAs, which hospitalizations would come fairly well -- would give an answer for in an RCT.

DR. SWENSON: Dr. Greene?

DR. GREENE: Although I have some concerns about being able to complete the study in a reasonable period of time, I think a randomized controlled trial, with the composite endpoint, would be the only real way to provide good data to answer it.

DR. SWENSON: Dr. Brittain?

DR. BRITTAIN: I favor the randomized studies to get unbiased estimates. And, clearly, for the composite, I think it's doable. And I think for the pooled -- when you pool the studies, you're going to be able to get reasonably good information on the extreme events.

DR. SWENSON: Dr. Kramer?

DR. KRAMER: I favor the randomized control

trial with the composite and the inclusion of the expansion, including noninvasive mechanical ventilation and ICU admissions.

I think that the randomized control trial should be done in a way that really challenges the usual way we've done them. I think accepting that they always have to be done in as cumbersome a way and as non-representative a way as they are happening now has got to change, and, actually, people in this room have some influence over that. So I would encourage that.

I'd also just like -- I just had some concerns, because I heard one of the comments that we should do the case control study first to see if there's a problem and then do a trial. And I would say the estimate for that study, I think even Dr. Carvalho would even agree, that it would be a minimum of 4 years, maybe 5 years, just to get that information and then you'd be doing a study on top of that, and it's going to be 10 years again and we're still asking these same question.

DR. SWENSON: Dr. Schoenfeld?

DR. SCHOENFELD: Well, by and large, I would favor a randomized control trial, although I'm a little bit concerned that the numbers don't seem to add up. If the risk is 1 in 3,000, and 6 million people are taking the drug in question, that would mean that 3,000 deaths a year are due to the drug in question. Then somebody else said that it was 10 patients die each day, I think it was. And so that would be about 3,000 patients die, all told.

So that kind of is a little bit concerning to me, that maybe the numbers -- if the risk we're trying to rule out doesn't have any kind of face validity given this, it may be that death is not -- there may be all kinds of things happening that I don't understand, but that's a little bit of a concern and I think that should be explored.

I think that the case control study is also a good idea. It does deal with smaller -- it can deal with smaller populations and so on. The big problem with it is it tends not to -- it might not answer the question sort of in a strong a way as a clinical trial would. I think that if, in fact, these drugs are

going to be used for a long time into the future, that that answer is necessary.

DR. SWENSON: Dr. Swenson. In principal, I support a randomized controlled trial on a larger composite endpoint. I think it is clinically relevant. Hospitalizations are important and if they're not the best surrogate for these adverse events, I think, in the real world, best case scenario, they serve us reasonably well. I'd support the trial.

Dr. Roberts?

DR. ROBERTS: I'm in favor of the nested case control study being conducted. I think it would inform the fatal asthma deaths quite well. It would be ideal to have, certainly, some of the other groups doing a clinical trial, as well, but I definitely would like to see this done.

DR. SWENSON: Dr. Ownby?

DR. OWNBY: It's, I think, impossible to argue against a randomized clinical trial, except I'm worried that to power it, the endpoints are going to be so diluted that it's not going to answer the

critical question. Therefore, I think in terms of feasibility, I would rather see a case control study, a nested control study in a sufficient cohort to get at the real critical issue of catastrophic events.

DR. SWENSON: Ms. Walden, we'd appreciate your opinion.

MS. WALDEN: Accepting that the endpoints are asthma-related death and intubations, I would support the case controlled study, especially if we have a situation where we have vulnerable populations or underrepresented populations, where a randomized controlled study would, I believe, leave that population out.

I think that there has to be a more direct approach to reach that population and I can't see an argument for a randomized controlled study in that perspective.

DR. SWENSON: Mr. Mullins?

MR. MULLINS: I believe the need for greater information and insight into this disease eclipses the challenges of conducting a randomized clinical trial. I believe we need greater insight into some of the

challenges around asthma in particular populations, pull out populations. I think we need greater insights into polymorphism. I think we need greater insight into some of the challenges around expanding the populations that are included in the study itself.

I would support a composite group of endpoints that include extended emergency room visits and other criteria that we've mentioned beforehand. Thank you.

DR. SWENSON: Dr. Rosenthal?

DR. ROSENTHAL: I'm in favor, in principle, in pursuing the randomized clinical trial approach, but for all the reasons that everyone else has mentioned around the table, I think we will end up needing to look at an expanded composite endpoint and more of a prolonged duration for the trial.

I think it's important for such a trial to be designed and powered to identify reasonable, but -- we might end up being -- as Dr. Fleming was saying yesterday, we may end up needing to design the study in such a way that we're looking for a slightly greater risk for some of these catastrophic endpoints

in order to make it feasible.

I also believe that a randomized trial would need to be designed in such a way that the at-risk subpopulations would be adequately covered. One advantage of the observational studies is that they can usually be done more quickly, and, in this case, it sounds like we lose that advantage.

So whereas observational studies are often quick and dirty, this design doesn't have the advantage of being quick. So that pushes me back toward randomized clinical trials.

DR. SWENSON: Dr. Joad?

DR. JOAD: I would like there to be a randomized clinical study, with the endpoint for adults being death and using the plan that Dr. Fleming has of combining the different drugs, the different companies, for that endpoint; and, for children, the endpoint being hospitalizations; and, then, definitely with enrichment for African-Americans.

For children and for African-Americans, I'd like to see a case controlled study and I would see that as an opportunity for everyone to really get at

having a balanced, diverse population of study subjects.

For case controlled studies, there are some issues with doing it, but if we could solve those issues, this would be a real opportunity to start solving issues of databases.

DR. SWENSON: Dr. Fleming?

DR. FLEMING: We often argue that our challenge, our responsibility is to provide not only for patients a choice, but to provide for them an informed choice. And we heard some very key adjectives for what should characterize the research we do.

We want it to be ethical. We want it to be feasible. We want it to be relevant. I would extend beyond that to say it really needs to be adequately reliable to address those issues that are most important to help guide caregivers and patients.

In that context, I think for where we are today, the randomized clinical trial is a very important component of what has to be done to be able to at least obtain a reliable assessment of the more

comprehensive composite endpoint effects, but to also provide very key added insights about the asthma-related death and intubation question as it relates to the addition of LABA to ICS.

That's not to say that there aren't additional elements that can be provided by other studies. Observational studies can be very useful. They can be very key for hypothesis generation, for providing supportive evidence.

I do agree with Dr. Joad, earlier on, that if, in fact, the true rates in the pediatric population for these catastrophic events is well below 1 in 10,000, then the observational study -- if, in that setting, we would need relative risks of much more than 10 to be important -- can be a very important added component to the overall research effort that we have to undertake.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: In a nutshell, both.

DR. SWENSON: Well, I want to take this opportunity to thank everyone on the panel for, I think, an excellent discussion, and discussions and

presentations from the sponsors and the FDA.

I think we could have the FDA give us some closing remarks. Dr. Rosebraugh?

DR. ROSEBRAUGH: Yes. I just wanted to take an opportunity to thank everybody again. I started this out by saying we really appreciate you all's input, and, again, we really do. It's very helpful for us to hear all of the opinions that everyone has, and there were a lot of opinions. So we'll have to go back and synthesize all that, but it's been very helpful. Thank you.

DR. SWENSON: Dr. Jenkins?

DR. JENKINS: If I could just add to that. This has been a great discussion and it's a discussion that emphasizes the challenge of these large comparative safety studies that Congress has now given us the authority to require, and it's a discussion that is kind of creating a new science and a new area of medicine that we're going to have to learn how to tackle and how to address.

I think you've seen, as you've gone around, these are very challenging questions when you're in an

environment where one group of people look at the data and conclude that there's no evidence of harm, so why bother doing a study, and another group of people look at the same evidence and say the harm is so great and so certain, that the drug should be removed from the market, and we're trying to utilize our authority to get an answer that more clearly defines those questions.

We're going to see this more, because we do have this authority now. And as I said, it puts tremendous responsibility on FDA to make sure that we design an appropriate study, with appropriate power, endpoints, all those parameters, so that, at the end, we get an answer that's useable.

We've seen this in the COX-2 arena. Dr. Fleming has mentioned several times the PRECISION study under the new authority, but it's clearly a study we've made clear to the company we want to see. There's been recent controversy in the media about the study for rosiglitazone, trying to assess the cardiovascular risks there.

So I'm hoping that when you see these

reports in the media, you will reflect back on your time for the last 48 hours, that these are very complex issues. They're not black-and-white.

We're trying to very responsibly use this new authority to require studies so we can get relevant, timely answers to these questions. And you guys have done a great job of providing input on that. I think we have a lot of very valuable comments that we can take back and try to put together a path forward.

So thank you so much.

DR. SWENSON: All right. With that, I hope that we've been the value that you needed, and I close this meeting and wish everyone a safe trip home.

[Whereupon, at 2:48 p.m., the meeting was adjourned.]